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MAY, 1928

ORIGINAL ARTICLES.

THE RESPONSE OF THE RETICULOCYTES TO LIVER THERAPY: PARTICULARLY IN PERNICIOUS ANEMIA.*

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and

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Introduction. Pepper,[1] in this journal, in 1875, and Cohnheim,[2] in 1876, maintained that the anemia of pernicious (Addisonian) anemia was dependent primarily upon disorder of blood formation. This has been our conception of the cause of the anemia. It was one of the reasons that led to the choice of a diet rich in liver for patients with pernicious anemia on the supposition that liver might supply material that would promote an adequate growth of the primitive blood cells that crowd the bone marrow in relapse. This idea is consistent with Whipple's[3] view that the cause of the anemia is dependent upon an improper or inadequate formation of the stroma of the red blood corpuscles. In the past fifty years many authorities have maintained that the bone marrow is deeply implicated in the disease process, but the view that the anemia is particularly dependent upon excessive destruction of red blood corpuscles has been the prevalent one. It is difficult to conceive that the prompt improvement in the health of patients with pernicious anemia which follows with regularity the feeding of adequate amounts of liver,[4, 5] or an

* The expenses of this investigation have been defrayed, in part, by a grant from the Proctor Fund of the Medical School of Harvard University, for the study of Chronic Diseases.

effective fraction of it can be attributed to stopping a hemolytic process. Even so, dysfunction of hemoglobin pigment metabolism, which may partially be due to abnormal red blood cell destruction, is a feature of the disease.

Peabody's[6] observations on the pathology of the bone marrow obtained by puncture of long bones indicate that the anemia has its root in a functional ineffectiveness of the bone marrow. During relapse, the primitive cells that crowd the marrow appear to fail to differentiate toward mature erythrocytes. During a remission, the histologic appearance of the marrow progressively changes toward normal. Peabody[6] has suggested that his observations indicate that it is very probable that liver feeding does promote the development and differentiation of mature red blood corpuscles. Our observations[7] upon the extraordinary, regular, prompt appearance of a temporary, marked increase of the young red blood cells, particularly reticulocytes (intermediate in immaturity between the nucleated erythrocyte and the adult normocyte) in the peripheral blood following the administration of large amounts of liver, also suggest that it causes a rapid maturation of primitive cells in the marrow and favors the conception that the anemia is primarily dependent upon an inadequate blood formation. Pernicious anemia, however, is more than a disease of the blood; it is a process that involves various tissues. The digestive and central nervous systems are also affected and are features as distinct as lack of blood.

Material and Methods of Study. It is the object of this communication to describe particularly the reaction of the reticulocytes to the feeding of liver and kidney. The nature of the material in liver that is specifically effective in pernicious anemia is considered elsewhere.[8]

The present study is concerned with the influence of this substance which apparently acts to promote the maturation of primitive bone marrow cells in pernicious anemia. Some of the information presented has been derived from observations on over 80 patients fed fractions of liver.* The particular facts concerning the effects of fractions of liver are presented in other papers.[8, 9] It may be stated here, however, that the response of the reticulocytes to the feeding of effective fractions or extracts of liver differs in no essential way from their response following ingestion of whole liver or kidney. The study of the feeding of liver and kidney is based upon 73 cases of pernicious anemia, 45 cases of "secondary" anemia and 8 normal persons.

* In an effort to determine the nature of the active principle effective in pernicious anemia Dr. Edwin J. Cohn and his collaborators, in the laboratories of Physical Chemistry of the Harvard Medical School, prepared the fractions of liver referred to. Later one of these fractions was manufactured for the Committee on Pernicious Anemia of the Harvard Medical School, by Eli Lilly and Company, of Indianapolis, and is known as "Liver Extract Number 343."

The percentage of reticulocytes in each individual's blood was determined before therapy was instituted. Sometimes this was done many times over an interval of from one to two weeks. After the treatment was begun, percentage counts were made daily until the reticulocytes returned to approximately normal. Fixed cover-glass smears of capillary blood stained with brilliant cresyl blue and counterstained with Wright's stain were employed. It is important that the staining be conducted so that all the reticulated red blood cells are stained and that distinct polychromatophilia does not appear. The use of buffered solutions of dyes will aid to insure proper staining. It is recognized that the counts of cells made in fresh preparations may yield more accurate results, but for practical purposes the fixed preparations are satisfactory. Counts on venous rather than capillary blood may perhaps permit slightly less error, but repeated counts on venous blood are impractical.

The reticulocytes in pernicious anemia usually comprise less than 3 per cent of the circulating red blood corpuscles and their absolute numbers are frequently less than in normal blood. Liver therapy is not the only cause for their temporary increase, for they may rise and fall "spontaneously" and following various therapeutic procedures, such as transfusion of blood, splenectomy and the administration of arsenical substances. The regularity with which the young red blood cells increase and the large numbers that appear in the blood stream in pernicious anemia following the ingestion of large amounts of liver, kidney, or but a few grams of an effective liver fraction, is however striking. The reaction has failed to occur but rarely and then special circumstances usually explained its absence.

The Typical Response of Reticulocytes in Pernicious Anemia to Liver. Typical responses of the reticulocytes to the feeding of 220 gm. of raw calves' liver pulp are illustrated in Fig. 1. Similar responses have occurred following the administration of cooked liver, liver broth, cooked and raw kidney, and certain fractions of liver. The percentage increase of the young red blood cells have been found to vary in a fairly regular manner with the level of the red blood cell count and with the amount of effective material fed. Variations also occur dependent upon the precise state of the patient, but only under unusual conditions have further variations of importance been recognized.

The data presented in Fig. 2 illustrate that the height to which the percentage of reticulocytes rises in the usual case (a few atypical responses are excluded) is in inverse relation to the level of the red blood cell count at the time therapy is commenced. This relation probably depends partly upon the smaller number of primitive cells in the marrow when the red blood cell count is high than when it is low. As a result more primitive cells are influenced by liver the lower the level of the red blood cells.

The study indicates that the absolute number of reticulocytes in

the blood at the peak of their rise in different cases treated with the same, but relatively large, amount of liver varies in the same direction but to a lesser degree than does their percentage number. These observations, which will subsequently be subjected to quantitative formulation,[9] suggest that the number of reticulocytes to enter the blood stream will be greater the more the bone marrow is filled with primitive erythrocytes. Each case with the same red blood cell level has not of course an identical amount of bone marrow

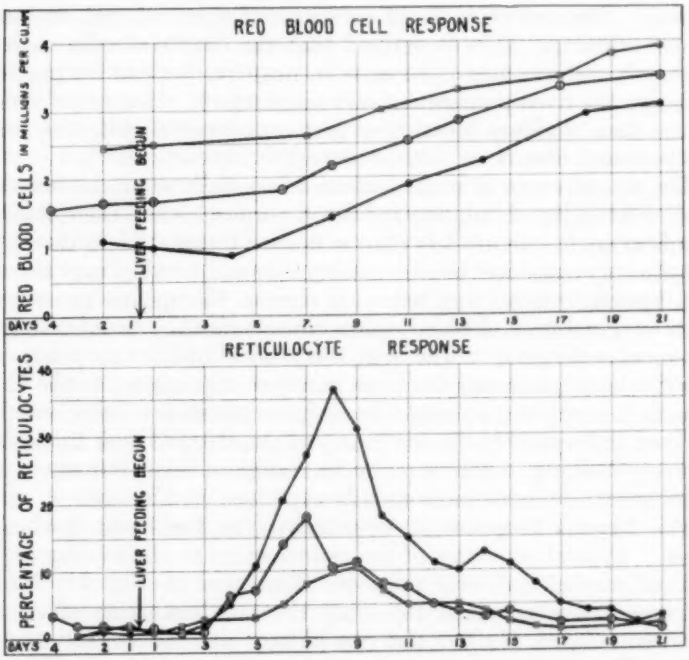

FIG. 1.—The effect on the reticulocytes in pernicious anemia of feeding daily 220 gm. of liver pulp to each of 3 patients with different red blood cell levels. The same type of line in each part of the figure records data for the same patient. In general, the highest blood cell count is accompanied by the lowest reticulocyte count and *vice versa*.

disorder. A certain maximum number of reticulocytes can be delivered from the marrow of any case, at least with a red blood cell count below 3 million per cu.mm. In some cases with a very similar number of red blood corpuscles, the same amount of liver or potent material it contains, will bring forth more reticulocytes than in others presumably because there are more primitive cells in the bone marrow in one than in the other case.

When the red blood cell count is about 3 million or more per cu.mm. liver feeding permits either no detectable response of the reticulo-

cytes or their absolute increase is relatively small compared to what occurs when the red blood cell count is low. This observation (illustrated in Fig. 2) furthers the idea that there is some relationship between the numbers of reticulocytes that will quickly enter the peripheral blood and the total number of primitive cells within the marrow.

When there are few primitive cells in the marrow, as occurs when the red blood cell count is high and the process of maturation is hastened by the influence of liver, probably relatively few cells are

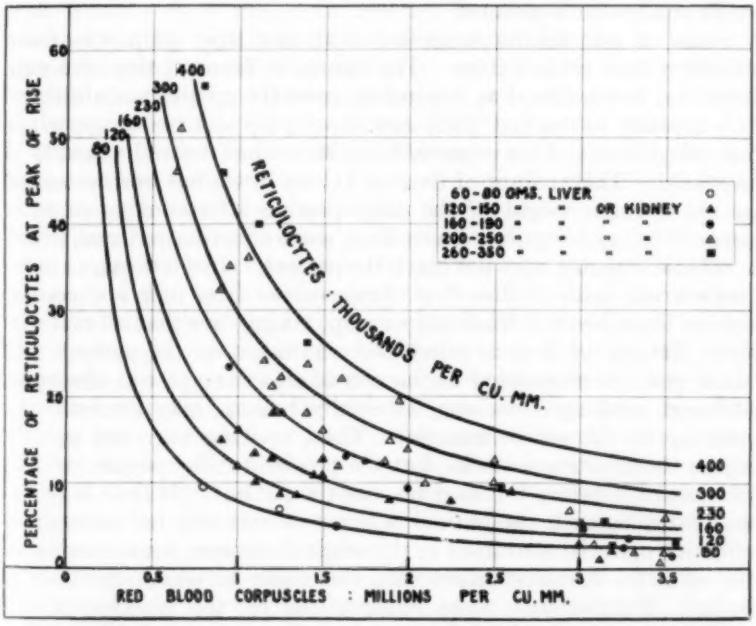

FIG. 2.—The height of the reticulocyte response at different levels of erythrocytes to the feeding of liver or kidney in cases of pernicious anemia. Cases giving atypical responses for reasons indicated in the text are excluded. The erythrocyte count given is the one before treatment was commenced. Thus, the absolute number of reticulocytes at the peak of their rise, usually from six to eight days after liver was first fed, would actually be greater than shown by the contour lines.

forced into the circulation in such immature forms as reticulocytes. In other words, when the marrow is not greatly crowded with primitive cells there is probably a better opportunity for the cells to complete their growth within the marrow and enter the blood stream in a relatively mature form. If the marrow is crowded with megaloblasts and the process of growth is enhanced, most of the cells immediately entering the circulation will be reticulocytes. On the other hand, when many of the cells in the marrow are normoblasts, and their growth is accelerated through the feeding of liver, it would

seem that but few of the cells will enter as reticulocytes, whereas the larger part will enter the blood with the histologic appearance of adult cells. These conditions in pernicious anemia may explain why the reticulocyte increase is temporary and why relatively few reticulocytes appear when the red blood cell count is relatively high. This conception is borne out by observations on the bone marrow by Peabody,[6] Castle[10] and ourselves. They show that as effective material from liver is fed the most primitive bone marrow cells decrease rapidly, normoblasts become relatively and actually greater in number and then gradually decrease to normal numbers as the patient's health is restored.

Some of our results suggested that raw liver pulp was more effective than cooked liver. The figures in favor of this idea can, however, be explained as dependent upon the greater variability of the amount of cooked than raw liver pulp derived from whole uncooked liver. This is particularly true when a small quantity is prepared. The amount of liver or kidney given has been recorded as the average weight of the daily portion after cooking or after preparation as raw pulp. In cooking, some effective material, which is soluble in water, may not reach the patient. In a few cases a comparison was made of the effect of raw calves' liver pulp and cooked calves' liver, broiled, fried and as soup, taking care that all material from 300 gm. of liver as purchased was taken by the patient. In these tests no undoubted distinction of effectiveness was observed, although prolonged cooking, especially boiling, may decrease the potency of the active material. Thus, cooking may not greatly injure the effective material, but the procedure may permit the loss of some of it before the food reaches the patient. If liver is boiled and eaten as such the patient will not receive the full amount of effective material contained in the original amount, because some of the effective material passes into the water in which the liver is boiled. Furthermore, from observations on the reaction of the reticulocytes, and rate of rise of the erythrocytes, no definite difference in effectiveness has been detected between cooked and raw kidney (lamb), liver of calf, beef, pig (fresh or canned), deer or sheep.

The characteristic reticulocyte response during the first three weeks of liver therapy, as shown in Fig. 1, is subject to certain variations. These are of relatively minor degree and dependent, apparently, upon the amount of material fed and the given state of the patient. The relative uniformity of the reaction is noteworthy. The rise of the reticulocytes tends to begin sooner and proceed more rapidly when the red blood cell count is low than high, and when large rather than small amounts of material are fed. When from 150 to 350 gm. of liver or kidney are fed daily, the onset of the reaction may be as soon as the third or rarely as late as the ninth day. Usually it begins before the seventh day. After liver or its equivalent is first given the peak of the reticulocyte increase usually

occurs between the sixth and the ninth day, seldom as soon as the fifth, or after the tenth day. Reticulocyte counts close to the maximum may occur on several days in succession, particularly when the dose of effective material is not maximal. The reticulocytes decrease at a somewhat slower rate than they increase. At first they usually fall rapidly and then more slowly. From the time they have definitely increased until they have returned to this same level, it is rarely less than seven or more than thirteen days, and usually about eight to ten days. Then their percentage frequently remains for a week or more somewhat higher than before treatment was begun. As a rule their reaction is completed within three weeks from the commencement of therapy. Finally, as the red blood cell count reaches high levels, the reticulocytes usually all but vanish, occasionally representing but 0.1 per cent of the red blood cells, equivalent to a low-normal or slightly subnormal value.

Changes in the Formed Blood Elements Accompanying the Response of the Reticulocytes. After liver, or the effective material it contains, is first fed and before the rise of the reticulocytes begins, there has often occurred a slight decrease in the red blood cell count. This may often be accounted for by alteration in the distribution of the body fluids, but would suggest the possibility that the effect on the bone marrow of the active principle in liver was the prevention of the premature expulsion of cells, rather than the probability that it speeds up or permits maturation. The corpuscles seldom can be detected increased when the reticulocytes have started to rise, but, as has been discussed,[8, 9] an increase approximately proportional to the number of reticulocytes in the blood is measurable at the time of the height of their rise. Then the ingestion of adequate daily amounts of potent material in liver allows the erythrocytes to continue to rise rapidly to normal.

Accompanying the response of the reticulocytes to the effective liver substance, it is the rule for the blood platelets and bone marrow white cells to increase. It is thought that these elements are permitted to do so particularly because the parent cells in the bone marrow are released from being encroached upon by the primitive erythrocytes, which rapidly decrease. Distinctly immature types of bone marrow cells and blood platelets may accompany the increase of reticulocytes in the circulating blood. If many nucleated red blood cells appear they are apt to reach the peak of their rise shortly before the time when the greatest concentration of reticulocytes occurs. The reticulocytes themselves decrease in size as their reaction proceeds and the erythrocytes increase.

The Response of the Reticulocytes in Pernicious Anemia when Small Amounts of Liver are Given. When small amounts of effective material are fed daily a delayed slow rise of reticulocytes of but a slight degree occasionally may be observed, which may persist for a longer time than when large amounts are fed. This suggests that

maturation of the cells in the marrow may proceed more slowly when the dose of effective material is slight, and, thus, the reticulocytes continue to enter the blood stream over a relatively long period of time. A similar state of affairs has been observed in two patients whose marrow is believed to have been damaged by repeated (over 30) transfusions of blood, yet who took large amounts (225 gm.) of liver. The reticulocytes of other patients, who have received many transfusions, have responded in the usual manner to liver therapy. In this connection, it is recorded here that one of us (Minot) has observed, prior to the days of liver therapy, that cases transfused with blood many times a year were very apt to have decreasing numbers of nucleated red blood cells in their blood stream at the same low red blood cell level the more often transfusion was performed.

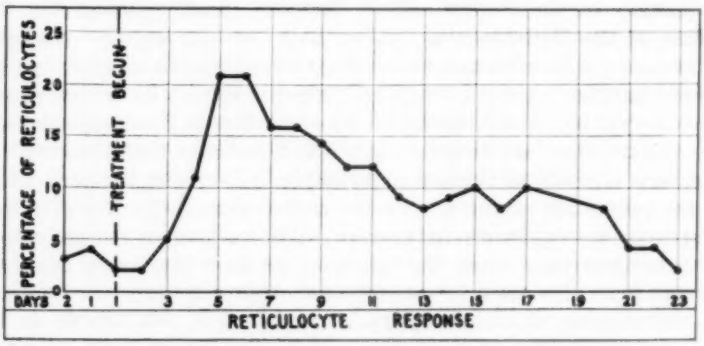

FIG. 3.—An unusual effect of feeding daily large amounts of potent material in liver in pernicious anemia.

The continuance for an unusual length of time of a relatively high level of reticulocytes does not necessarily mean that a small amount of potent material in liver has been given. When large amounts are fed one may rarely observe, following a rapid rise, the reticulocytes to take the course illustrated in Fig. 3. Such a reaction causes the percentage of reticulocytes at the peak of their rise to not fall in line with the usual case.

Another effect of the daily feeding of a small amount of liver is that although a characteristic reaction of the reticulocytes develops, it may be of small magnitude. This may be followed by either a very slight or no appreciable rise in the red blood corpuscles. Under these circumstances, if some days after the reticulocyte reaction is complete, the amount of liver fed daily is increased markedly, one may observe a second characteristic reaction of the young red blood cells, comparable to that occurring in other patients originally given a similar large amount of liver. Then the total number of red blood

cells will be observed to rapidly increase. Fig. 4 illustrates this combination of circumstances.

The influence of increasing a given dose of liver material may be demonstrated in still another manner. If the daily amount of substance fed has produced somewhat less than a maximal effect upon the reticulocytes and the quantity is increased to a very large amount soon after the reticulocytes have started to fall, there may occur a

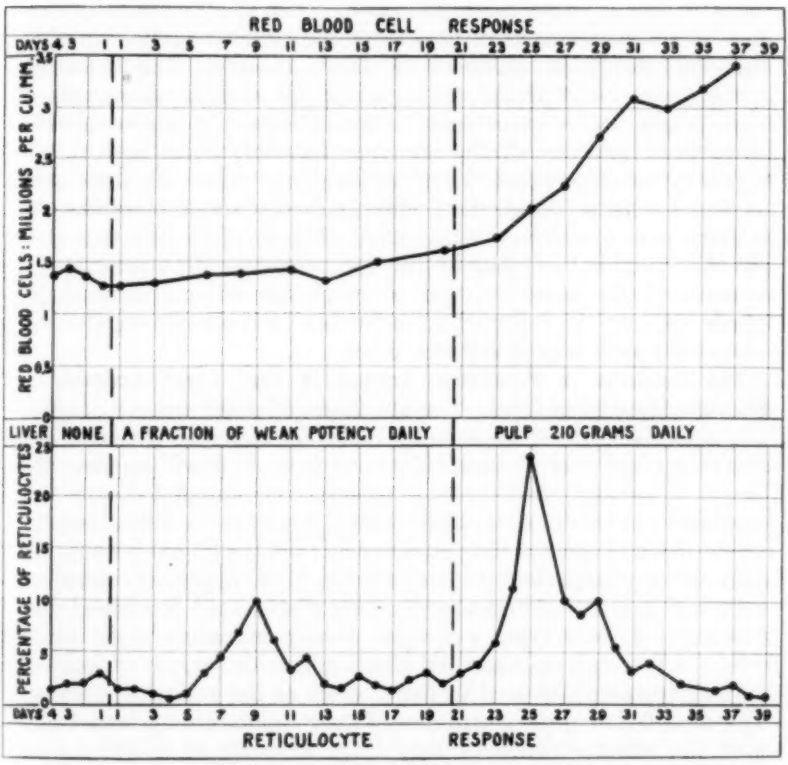
RED BLOOD CELL RESPONSE
DAYS 4 3 1 1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39
RED BLOOD CELLS: MILLIONS PER CU. MM.
LIVER NONE A FRACTION OF WEAK POTENCY DAILY PULP 210 GRAMS DAILY
PERCENTAGE OF RETICULOCYTES
DAYS 4 3 1 1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39
RETICULOCYTE RESPONSE

FIG. 4.—An effect produced by feeding first a small and then a relatively large amount of potent material in pernicious anemia.

secondary, but slighter, rise. The subsequent fall of the reticulocytes to normal may then proceed more slowly than if the original daily dose had been continued. If, however, the original amount given daily is far short of that which can produce a maximal effect, the secondary rise of the reticulocytes resulting from the addition of a large amount of liver, will be one of a greater magnitude than the primary response. When an additional amount of liver is given before the reticulocytes have reached normal, or when they have

only just done so, their response to the extra amount of potent material will usually occur sooner than when an equally large amount is given a patient, who has taken no liver. There is apparently some minimal amount of liver in the vicinity of 60 gm. of cooked liver, which is a necessary daily amount to produce a distinct reticulocyte reaction when the red blood cells are about 1.25 million per cu.mm. This circumstance and the fact that a secondary rise of reticulocytes can occur when the quantity of liver is increased, suggests that effective material may be given in an amount to produce some development of growth of the primitive cells, but that that daily dose is not sufficient to cause a complete transformation of the marrow. A prolonged, sustained rise of the reticulocytes of but a slight degree may result, however, from the ingestion of a daily small quantity of effective liver material, which may be followed by no subsequent rise of reticulocytes when the amount is increased. Small doses, thus, may gradually act to complete the reaction over a relatively long period of time. It is also true that less than maximal amounts of liver frequently permit a reticulocyte response of the usual duration, although one of small magnitude, which may not be followed by a further increase of reticulocytes when additional potent material is fed.

The Influence in Pernicious Anemia of Very Large Amounts of Effective Material in Liver. The maximum effective amount of effective material in liver apparently varies for different patients, and it is recognized that whereas 125 gm. of liver daily will improve the health of patients, and do so sometimes very rapidly, double this amount is essentially always followed by very rapid beneficial results. In the blood of some of the patients who took the largest amounts of liver, or very large doses of liver extract, there appeared coincident with the increase of reticulocytes many nucleated red blood corpuscles of various types and some grossly immature white blood cells. A few such cells and red blood cells with various varieties of nuclear remains appeared in many cases as the reticulocytes rose. This association of the occurrence of many immature nucleated cells with the administration of very large amounts of effective liver material suggests that perhaps excessive dosage is undesirable because of a tendency to permit delivery from the bone marrow of very immature products. Even so, when many nucleated cells have appeared, the numbers of reticulocytes have been distinctly great and the patient's red blood cells have increased at a maximal rate. This type of reaction is in contrast to a common sort of "blast crisis" which occurs in the natural course of the disease. Under these circumstances, the appearance of many immature nucleated blood cells more often heralds downfall than improvement in the patient's health. In such reactions, the reticulocytes often are relatively few compared to the nucleated cells, which is in contrast to the relatively very large numbers that appear when the blood contains many

nucleated cells soon after liver therapy is begun. This latter sort of response of the bone marrow may rarely occur spontaneously and often after splenectomy;[11] and when it does, improvement in health follows it with the same regularity as when adequate liver therapy is instituted. The cause for the frequent slight and rare pronounced, "spontaneous," temporary rises of reticulocytes and those following splenectomy and transfusion of blood might lead to interesting speculations.

An exceedingly rapid and very intense reaction of the reticulocytes and other formed bone-marrow elements, accompanied by an extraordinarily rapid rise of red blood cells, may perhaps take place if the patient is given a very large dose of effective liver material, coincident with the onset of a spontaneous remission. In one case, this took place when there had developed rapidly from the liberated hemoglobin a great excess of bile pigments in the circulation, a state of affairs which produces a stimulus to the bone marrow.

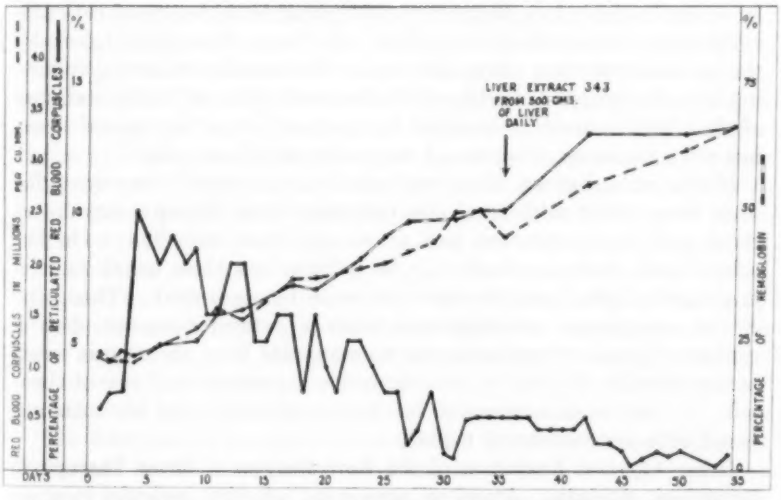
LIVER EXTRACT 343 FROM 500 GMS. OF LIVER DAILY
RED BLOOD CORPUSCLES IN MILLIONS PER CU. MM.
PERCENTAGE OF RETICULATED RED BLOOD CORPUSCLES
PERCENTAGE OF HEMOGLOBIN
DAYS

FIG. 5.—A prolonged "spontaneous" increase of reticulocytes; a rare condition, followed by no further rise of these cells when a maximal amount of liver extract was given.

The Influence of "Spontaneous" Increases of Reticulocytes upon their Reaction to Liver Therapy. A few patients were first treated with liver or its equivalent when they had a considerable "spontaneous" increase of reticulocytes. There were in the blood from 150,000 to 300,000 per cu.mm. (from 8 to 23 per cent of the erythrocytes). The feeding of 225 gm. of raw liver pulp to one of these patients was begun two days after the reticulocytes started to decrease. This produced no secondary rise of these cells, which progressively, but slowly, fell to normal as the red blood cell count rapidly rose.

Similar results have been observed in three other cases, and would point to the similarity of mechanism in the onset of spontaneous remissions and the improvement following liver feeding.

In another case (Fig. 5) there was a sudden mysterious increase of reticulocytes possibly dependent upon the patient eating during the preceding days much more food than she had for some weeks. Then for about a month, while she was given no particular treatment, the reticulocytes were daily approximately 100,000 per cu.mm. During this time the red blood cell count increased from 1 to 2.5 million per cu.mm. At the end of the month there was given daily an amount of liver extract at least as effective as 240 gm. of liver pulp, which was followed by no further rise in the reticulocytes, although they continued slightly increased for about ten days more. The red blood cells, however, increased 1 million per cu.mm. in the twenty days after the extract was first given.

These observations suggest that something had spontaneously supplied a maximal effect on the primitive cells in the bone marrow. In several other cases there were considerable increases of reticulocytes when they were first treated. In these, the course taken by the reticulocytes was either similar to that usually observed following liver therapy, or else like that observed when an additional dose of the effective material is added to an amount that has caused some, but not a maximal, response of the young red blood cells.

If the reticulocytes have continued to be slightly increased for some time, their additional rise following liver therapy may be as great as if their numbers had previously been very few. On the other hand, their increase may be a little less than usual when a prolonged slight "spontaneous" increase has occurred. Thus, one of the exceptional circumstances when a patient does not show a typical response of reticulocytes to adequate liver therapy is when he is treated in the face of a considerable "spontaneous" rise of these cells or when such a response has been completed and his total red blood cells are increasing rapidly.

Other Atypical Responses of the Reticulocytes to Liver Therapy in Pernicious Anemia. Atypical responses of the reticulocytes to adequate amounts of liver have been mentioned and are rare. The other instances of atypical reactions that have been observed are noted below. Delayed and weak responses of the reticulocytes occurred in two patients with a severe complicating infection. In turn the red blood cells counts rose unusually slowly. Infectious processes can depress marrow function and it has been pointed out previously[5] that they may account for decreases in the red blood cell count after it has risen above 4 million per cu.mm. Although infections may act to inhibit the reticulocyte response and delay the rise of the red blood cells, such, however, is not always the case. In several patients with infections, including one with bronchopneumonia, and gangrene of the lung, a marked prompt response of

the reticulocytes occurred, although the patient mentioned died soon after these cells had passed the peak of their rise.

The occurrence of delayed though prolonged responses of the reticulocytes, which did not reach a high level, has been referred to as occurring in 2 cases that previously received over thirty transfusions of blood. In these cases the red blood cells increased to over 4 million per cu.mm. unusually slowly. In another patient who had received 25 transfusions of blood, but whose case was complicated by various conditions, the reticulocytes responded to the daily feeding of 200 gm. of liver pulp briefly and trivially, when the red blood cells were about 2 million per cu.mm. This patient's condition and response to therapy has been peculiar in numerous ways, and although the red blood cells reached about 4 million per cu.mm. four months after taking large amounts of liver daily, they showed no definite increase for many weeks after the treatment was begun.

In one patient first treated for three weeks with a fraction of liver, and then with 200 gm. of raw liver pulp a day, there occurred during the six weeks of observation no distinct rise of the reticulocytes. During this time, the red blood cells remained about 2 million per cu.mm., but, four weeks after first taking the pulp were 2.7 million per cu.mm. The cells then rapidly increased and have remained in the vicinity of 5 million for the past six months. No definite explanation is apparent for the slow rise of the corpuscles or the lack of a response of the young red blood cells. These last 2 cases referred to stand out as distinct exceptions to the rule that when the red blood cell count is below 3 million per cu.mm. an intense response of the reticulocytes occurs promptly when effective material is fed in adequate quantity, provided such special circumstances as indicated above are not present. It is emphasized here that except for the cases mentioned, over 150 cases consecutively treated by an adequate amount of liver, kidney, or potent extract of liver have shown a prompt and very definite response of the reticulocytes.

The Reticulocyte Response when the Red Blood Cell Count is High in Pernicious Anemia and in Normal Persons. The relatively slight, or lack of distinct, increase of the reticulocytes when the red blood cell count is about 3 million or more per cu.mm. is real, and not simply apparent because of the occurrence of a small percentage of reticulated red blood cells. Very excessive amounts of potent liver material have not been given patients with high red blood cell counts. Such doses might affect them differently than when adequate quantities are given. When the red blood corpuscle count is high there sometimes occurs for a number of days after about 225 gm. of liver are fed, or when after small amounts an additional quantity is taken, an increase of reticulocytes from less than 1 per cent to a little over this percentage. Frequently there is no detectable change in their numbers. At other times, a distinct characteristic response may be witnessed, if the count is about 3 million per cu.mm. One might

thus suppose that since the state of the bone marrow in pernicious anemia approaches normal when the red blood cell count is high that there would be no respone of the reticulocytes to liver therapy in normal persons, or in those whose marrow was not crowded with such primitive red blood cells as occurs in pernicious anemia in relapse. Such appears to be the case from the observations recorded herewith.

Liver feeding for from three to five weeks produced in 5 healthy young men and 3 normal women no abnormal changes in the numbers of reticulocytes. Three of these individuals took daily about 150 gm. of cooked liver and the other 5 ate about 240 gm. a day. There was a slight increase in hemoglobin in 4 of these persons and the data suggest a trivial increase in the number of corpuscles in the 3 whose red blood cell count was the lowest (about 4.5 million per cu.mm.) at the beginning of the experiment. Although liver feeding does not increase the reticulocytes in normal persons, large numbers can appear in a healthy person's blood stream. This takes place when there is an increased oxygen want of the bone marrow, as occurs upon ascending to high altitudes.

The Reticulocyte Response in Other Anemias than Pernicious Anemia. A marked reticulocyte response to liver therapy may occur in other cases of anemia than pernicious anemia, but this is at least rare in cases of ordinary secondary anemia. During the first two to three weeks no changes undoubtedly attributable to treatment have been observed in the daily number of reticulocytes in 28 cases of secondary anemia given from 150 to 240 gm. of liver a day. The figures for the reticulocyte percentage in 3 of these cases ((1) unexplained anemia, (2) cirrhosis of liver, (3) "chronic chlorosis with achylia gastrica") suggest that they might be interpreted to indicate that a very slight but irregular increase (from about 1 to 3.5 per cent) was due to the influence of liver feeding. In 14 of the 28 cases the red blood cell count was above 3 million per cu.mm.; in 7 of these they were above 4 million per cu.mm. The hemoglobin was between 35 and 45 per cent in 4, and between 60 and 75 per cent in the other cases. The causes of the anemia were as follows—chronic blood loss, 5; cancer, sepsis and unexplained, 2 of each; cirrhosis of the liver, colitis, "chronic chlorosis with achylia gastrica," 1 of each. In the remaining 14 cases the red blood cells were less than 2.8 million per cu.mm. and the hemoglobin below 50 per cent. In 4, the count was below 1.6 million per cu.mm. The anemia was due to chronic blood loss in 4, to leukemia of various types in 4, and in 5 other cases associated with one of the following conditions; cancer, multiple myeloma, lymphoblastoma, sepsis and pregnancy. The last case to be accounted for was peculiar and resembled chronic acquired hemolytic jaundice. Although definite response of the reticulocytes did not occur in these 28 patients fed large amounts of liver, the treatment was accompanied by distinct improvement in

the health of a few. However, the treatment of "secondary" anemia is not for discussion here. Nevertheless it is noteworthy that the patient with a condition resembling acquired hemolytic jaundice had been anemic for many months and had at the time treatment was begun about 200,000 reticulocytes per cu.mm. in her blood, and that these cells decreased rather rapidly as her red blood cell count rose to normal.

One case of Hodgkin's disease with a red blood cell count of 2.5 million per cu.mm. treated with large amounts of liver daily showed a slight irregular increase of reticulocytes reaching 6 per cent eleven days after treatment was begun. There was no significant increase in the hemoglobin or red blood cells at the end of four weeks. It is possible to attribute this reticulocyte increase to other causes than the feeding of liver.

Eleven other cases of anemia, not ones of pernicious anemia, have shown no response of the reticulocytes to the feeding of a fraction of liver in doses that are promptly effective in pernicious anemia, and none of these patients showed in three weeks any improvement that could be attributed to the substance. These were cases of (1) anemia associated with pregnancy, hemoglobin 55 per cent, red blood cells 4.5 million per cu.mm., (2) chronic blood loss, (3) infectious endocarditis, (4) cancer of the colon. In these last 3 cases the red blood cells were about 3 million per cu.mm. and the hemoglobin about 50 per cent, (5) and (6) aleukemic myelosis, (7) atypical "splenic anemia" in a child, (8) a similar case upon which splenectomy had been performed, (9) lymphatic leukemia, (10) aplastic anemia, (11) myelogenous leukemia. In these last 6 cases the red blood cells were from 2.2 to 0.6 million per cu.mm. and the hemoglobin from 50 to 15 per cent.

Another group, composed of 10 cases of secondary anemia, was treated with such amounts of liver extract as are maximal for pernicious anemia. Eight of these 10 showed temporary slight increases of reticulocytes to not over 3.7 per cent. In the other 2 cases the red blood cells were 2.1 and 3 million per cu.mm. and the maximal reticulocyte percentage was 6 and 8 respectively. The anemia in both cases was chronic and associated with indigestion and in the former abnormal blood loss from the pelvis was a factor. In 6 of the other 8 cases the anemia was associated with either myxedema, pituitary disease, chronic arthritis or colitis. In the remaining 2 cases the anemia was not adequately explained. In these 8 cases the red blood cells were in the vicinity of 3 million per cu.mm. and the hemoglobin concentration proportionately lower, except that in one woman, aged fifty years, with unexplained anemia of long duration the red blood cell count was 4.8 million per cu.mm. and the hemoglobin 50 per cent. In cases of pernicious anemia with similar red blood cell counts one would expect no greater rise of the reticulocytes, but prompt and distinct symptomatic improvement.

Some of these cases of "secondary" anemia showed no symptomatic improvement and in others the anemia became somewhat less. In this connection it may be noted that the influence of feeding large amounts of liver, or liver extract, with large doses of iron can produce sometimes a desirable effect in cases of "secondary" anemia which is not observed from the administration of either alone.

Although many cases of "secondary" anemia have shown either no response, or but slight response, of their reticulocytes to liver therapy, a response entirely like that seen in pernicious anemia with a rapid increase of red blood cells to normal has been observed in 5 unusual cases with considerable anemia, but clearly not cases of pernicious anemia. The nature of the conditions these patients had was such that it is not an unreasonable assumption that their bone marrow may have simulated that of pernicious anemia in relapse, and it was proved by bone marrow puncture to be of this type in the second case referred to below.

The 5 cases may be briefly characterized as follows: Two of the 5 patients had no well recognized cause for their anemia and their red blood cells were reduced somewhat more than 50 per cent below normal. Achlorhydria was not present. The histologic picture in one simulated that of pernicious anemia, but the icterus index was normal and the individual had neither the tongue nor neural symptoms characteristic of pernicious anemia. He had partaken for years of an abnormal diet which we believe played an important rôle in the production of his illness. The other case had had anemia for over three years and many physicians in different parts of the world have unanimously agreed that the blood picture was that of "secondary" anemia, although it had some of the features of pernicious anemia. The average diameter of the red blood cells was normal when the count was 2 million per cu.mm.

The third unusual case that developed a reticulocyte response had a blood picture of "secondary" anemia with a color index close to 1 and a red blood cell count of 2.7 million per cu.mm. Her reticulocytes rose to 11 per cent. This woman gave a history of having taken for years a peculiar diet and of suffering from "colitis" without diarrhea. She had had lesions on the back of her hands simulating those of pellagra. Achlorhydria was present.

The 3 patients mentioned were treated with about 200 gm. of liver pulp a day and improved about as promptly and rapidly as simularly treated cases of pernicious anemia. The same sort of improvement took place in 2 cases whose anemia became severe in association with pregnancy and that were treated with adequate amounts of liver fraction and showed promptly a definite response of the reticulocytes. These patients had apparently been somewhat anemic for years and it is known that one had achlorhydria and a slightly enlarged spleen. Their blood picture did not resemble that of pernicious anemia in spite of the red blood cell counts being less than 2.5 million per

cu.mm. and the color indices close to 1. There appears to be no precise name for the condition these patients had but it was obviously a different one from pernicious anemia.

It is to be noted that these 5 atypical cases of anemia, who showed a response of their reticulocytes entirely like that seen in pernicious anemia, resembled this disease in that it is reasonable to attribute their anemia to a primary disorder of blood formation. This may have been enhanced in 2 cases by pregnancy.

Sprue resembles pernicious anemia in various ways and it is known that liver therapy has been beneficial for these patients. In sprue, anemia may develop which simulates in all respects that of pernicious anemia and these patients' bone marrow may appear like that in the latter disease. We have treated one case of sprue with 200 gm. of liver a day. She has improved extraordinarily in every way, and her reticulocytes responded entirely like those of pernicious anemia cases. In order to learn further about the beneficial effects in sprue Dr. E. J. Wood was supplied by the Committee on Pernicious Anemia of the Harvard Medical School with some of the extract of liver effective in pernicious anemia. He has reported to us that the 2 cases so far treated have shown a striking, prompt response of their reticulocytes, rapid rise in their red blood cells, and extraordinary improvement in health. Bloomfield and Wyckoff[12] obtained the same result in a patient with sprue fed large amounts of liver. It is also to be expected that in other anemias, resembling idiopathic (Addison's) pernicious anemia, such as that which may occur with infection due to the fish tapeworm (Dibothriocephalus latus) an intense response of the reticulocytes with rapid rise of the red blood cells will occur following adequate liver therapy. Drs. W. J. Kerr and E. H. Falconer have kindly informed us that they have observed exactly this state of affairs. There are probably cases of other sorts of anemia than those reported upon in this study that can give a marked reticulocyte response to liver therapy.

Concluding Remarks. In pernicious anemia in relapse the reaction of the reticulocytes is apparently due to a specific action of the effective material contained in liver and kidney, and although the potent material can produce such a result in other conditions, it often does not do so in cases of ordinary "secondary" anemia. The other anemias in which liver therapy has permitted both the reticulocytes to respond distinctly and the red blood cells to rise rapidly may indeed have a type of distorted blood formation that approaches in character that of pernicious anemia. In pernicious anemia and these other anemias it seems that the reticulocyte reaction indicates that the specific substance acts particularly to promote the growth of the primitive cells crowding the bone marrow, probably by allowing their better maturation, and appears to be one that transforms a "megaloblastic" marrow to a "normoblastic" one.

Summary. The anemia of pernicious anemia is primarily dependent upon the failure of the primitive cells in the bone marrow to differentiate toward mature erythrocytes.

In pernicious anemia there occurs with extraordinary regularity a prompt, temporary, pronounced increase of the reticulocytes in the peripheral blood following the administration of large amounts of liver, kidney or potent fractions of liver. The number of reticulocytes usually remains definitely elevated for about nine days.

The reticulocyte response, which has been studied in more than 150 cases of pernicious anemia, is ascribed to the specific active principle effective in pernicious anemia promoting the growth of the primitive cells that crowd the bone marrow in relapse, probably by hastening or permitting their maturation.

The height to which the percentage of reticulocytes rises in the usual case is in inverse relation to the level of the red blood cells. Cases with more than 3 million red blood cells per cu.mm. exhibit never more than a slight response of the reticulocytes. In essentially all cases however, treated with adequate amounts of active principle, the red blood cells rapidly increase to normal.

Accompanying the response of the reticulocytes other immature types of formed bone marrow elements may appear in the blood and the white blood cells and platelets increase in numbers. Very large amounts of effective material may favor the appearance of many immature bone marrow cells.

Small amounts of effective material, or complications of the disease, may cause only a slight rise of the reticulocytes which may be delayed.

When submaximal quantities of liver have been fed the effect of additional amounts will be reflected in the course taken by the reticulocytes. A weak response may not soon be followed by significant increase of the total number of red blood cells.

If treatment is commenced when there is a considerable spontaneous increase of reticulocytes, or when this has just occurred, no subsequent rise of these cells may follow.

The feeding of large amounts of liver produces no response of the reticulocytes in *normal* persons.

Liver therapy in many cases of "secondary" anemia is a different matter than the treatment of pernicious anemia.

A reticulocyte response to liver therapy may occur in other cases of anemia than pernicious anemia, but it is absent or slight in ordinary cases of "secondary" anemia. Some unusual cases and some cases of anemia associated with pregnancy have shown a marked response of the reticulocytes like that seen in pernicious anemia. This has also occurred in sprue and in anemia due to the fish tapeworm.

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TREATMENT OF PERNICIOUS ANEMIA WITH LIVER EXTRACT: EFFECTS UPON THE PRODUCTION OF IMMATURE AND MATURE RED BLOOD CELLS.*

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The nature of the material in liver effective in pernicious anemia, and the character of the physiologic responses that it initiates, were brought into question by the knowledge that regular and strikingly beneficial results follow promptly the feeding of large amounts of liver or of kidney to patients with pernicious anemia.[1,2] The amount

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of potent material in these, and perhaps in other organs or foods, constitutes but an insignificant part of their bulk. The chemical fractionation of liver has rendered it certain that the active principle effective in pernicious anemia is neither protein, carbohydrate nor lipoidal in nature, nor is it apparently any of the known vitamins. The substance, or substances, whose nature has been considered elsewhere[3] is presumably a nitrogenous base or polypeptid. The extraction from liver of fractions containing this substance has simplified treatment and rendered it possible widely to vary, and accurately to control, the amount of active principle ingested. In the present communication there will be considered first such responses of the red blood cells to liver therapy as may be quantitatively formulated. The treatment of the disease by means of potent extracts of liver will then be considered.

In pernicious anemia stimulation of blood formation invariably follows promptly upon the feeding of any of the tissues, or extracts, that contain the active principle. The first important manifestation of the response is the appearance of greatly increased numbers of immature erythrocytes in the peripheral blood, particularly the reticulocytes. The response of the reticulocytes has been discussed in a previous communication.[4] Their delivery into the circulation is attributable to a rapid development of the primitive cells that crowd the bone marrow in relapse. The reticulocytes usually begin to increase in the blood in from three to eight days after therapy is begun. Their number usually continues to increase in the subsequent three to six days, when a maximum is reached. Thereafter, although the total number of erythrocytes steadily increases, the number of reticulocytes diminishes, until within from two to three weeks after the beginning of treatment relatively few occur in the peripheral blood. Since the erythrocytes continue to appear in large numbers after the peak of the reticulocyte rise, it must be assumed that sufficient time has elapsed after the feeding of liver, or kidney, or of liver extract, so that chiefly mature erythrocytes are extruded from the bone marrow.

The condition of the bone marrow as determined by the numbers of the different types of cells it contains, must be expected to influence the response of the patient. This can vary considerably in patients whose cases appear clinically very similar. The reaction of the reticulocytes to the material effective in pernicious anemia, which has been qualitatively described,[4] appears to be related quantitatively both to the amount of potent material fed and to the concentration of red blood cells at the time that the treatment is begun. Such generalizations, concerning the response to the active principle effective in pernicious anemia, as have resulted from our experience will presently be considered.

The Clinical Material and the Chemical Fractions of Liver Studied. The data that are sufficiently complete to warrant their use in the

following formulation are of four kinds: (1) Those derived from the critical study of 75 among the more than 150 cases treated with liver or kidney. (2) Those derived from the feeding of those fractions of liver prepared by one of us (Cohn) in order to determine the nature of the active principle.[3] (3) Those derived from the feeding of the extracts first manufactured in order to modify for large scale production the procedures evolved in the laboratories of physical chemistry of the Harvard Medical School. These were prepared for the Committee on Pernicious Anemia of the Harvard Medical School by Eli Lilly and Company of Indianapolis. And, finally, (4) those derived from the study of the cases given the extract made by this company which was finally chosen by the Committee on Pernicious Anemia as satisfactory for general distribution. This standardized product is known as liver extract No. 343, and although far less pure than has been produced, resembles "Fraction G" isolated while attempting to learn the exact nature of the effective material.[3] Over 160 cases have been treated by means of liver extract in the 13 clinics that have collaborated with the committee in estimating its therapeutic value. Sixty-five of these cases have been studied in Boston. Eighty-nine cases that supply the data upon which the following analyses depend have been treated with liver extract 343. The amounts given daily have usually varied from the extract derived from 300 to 600 gm. of liver. A few cases have been given daily extract from 800 to 1200 gm. of liver. The amount of this extract given has, therefore, varied usually from about 10 to 20 gm. per day. The results obtained from the study of these 89 cases reveal most satisfactorily some of the relations which have been observed in a much wider series of cases, in part because of the uniformity of the product, and in part because of the adequacy of the dosage. The studies of these cases have been made by many different persons. This circumstance may explain certain lesser variations. Data have been excluded when it appeared that obvious errors existed; as, for example, when the initial erythrocyte level appeared inconsistent with the subsequent counts. A few unusual cases also have been excluded for reasons described in the preceding paper; for example, patients first treated when a considerable concentration of reticulocytes was present in the blood stream. Thus, those few cases that presented complicated blood pictures are not considered in this paper, where the usual response of the reticulocytes is described.

The Relation between the Erythrocyte Level and the Percentage of Reticulocytes in the Blood at the Peak of their Rise. The level of the red blood cells, just before treatment is begun, bears a relationship to the state of the bone marrow, and shows a partial correlation with the reticulocyte response. This relation was also manifested by the response of patients fed very different amounts of liver as is indicated in the previous communication.[4] The results obtained when only

TABLE I.—THE RETICULOCYTES AT THE PEAK OF THEIR RISE FOLLOWING THE DAILY FEEDING OF ADEQUATE AMOUNTS OF STANDARDIZED LIVER EXTRACT.

Reticulocytes at peak of rise.* r (per cent).	Concentration of erythrocytes before treatment. E_o (millions per cu.mm.).	Concentration of erythrocytes at peak of rise of reticulocytes. E_p (millions per cu.mm.).	Increase in erythrocyte concentration at peak of reticulocyte rise. $E_p - E_o$ (millions per cu.mm.).	Concentration of reticulocytes at peak of rise (observed). $E_p r$ (millions per cu.mm.).	Concentration of reticulocytes at peak of rise (estimated). $\frac{E_o r}{1-r}$ (millions per cu.mm.).
37	0.50	1.30	0.80	0.48	0.29
56	0.65	1.47	0.82	0.82	0.83
49	0.60	1.20	0.60	0.59	0.58
46	0.60	1.20	0.60	0.55	0.51
46	0.60	1.00	0.40	0.46	0.51
39	0.60	1.30	0.70	0.51	0.38
31	0.82	1.18	0.36	0.37	0.37
46	0.90	1.60	0.70	0.74	0.77
43	0.90	1.50	0.60	0.65	0.68
40	0.95	1.30	0.35	0.52	0.63
43	0.95	1.30	0.35	0.56	0.72
Average when E_o was less than 1.0					0.57
33	1.09	1.63	0.54	0.54	0.54
31	1.00	1.30	0.30	0.40	0.45
21	1.00	....	....	....	0.27
39	1.05	1.80	0.75	0.70	0.67
30	1.10	1.65	0.55	0.49	0.47
26	1.10	1.40	0.30	0.36	0.39
24	1.10	1.40	0.30	0.34	0.35
24	1.10	1.55	0.45	0.37	0.35
29	1.20	1.60	0.40	0.46	0.49
28	1.30	....	....	....	0.51
27	1.20	....	....	....	0.44
20	1.20	1.70	0.50	0.34	0.30
Average when E_o varied from 1.0 to 1.2					0.44
26	1.21	1.66	0.45	0.43	0.43
25	1.22	1.56	0.34	0.39	0.41
46	1.30	1.80	0.50	0.83	1.11
27	1.30	....	....	....	0.48
24	1.30	1.55	0.25	0.37	0.41
24	1.30	....	....	....	0.41
23	1.30	1.70	0.40	0.39	0.39
22	1.30	2.00	0.70	0.44	0.37
16	1.32	1.80	0.48	0.29	0.25
23	1.35	.....	....	....	0.40
Average when E_o varied from 1.2 to 1.4					0.47
34	1.40	2.10	0.70	0.71	0.72
27	1.40	1.80	0.40	0.49	0.52
27	1.40	....	....	....	0.52
23	1.40	....	....	....	0.42
20	1.40	1.80	0.40	0.36	0.35
23	1.45	....	....	....	0.43
Average when E_o varied from 1.4 to 1.5					0.49
28	1.50	....	....	....	0.58
24	1.50	1.90	0.40	0.46	0.47
19	1.50	1.75	0.25	0.33	0.35
14	1.60	2.40	0.80	0.34	0.26
24	1.60	....	....	....	0.51
20	1.60	....	....	....	0.40
19	1.60	....	....	....	0.38
16	1.60	2.00	0.40	0.32	0.31
13	1.60	....	....	....	0.24
Average when E_o varied from 1.5 to 1.6					0.39

TABLE I.—THE RETICULOCYTES AT THE PEAK OF THEIR RISE FOLLOWING THE DAILY FEEDING OF ADEQUATE AMOUNTS OF STANDARDIZED LIVER EXTRACT.—(*Continued.*)

Reticulocytes at peak of rise.* r (per cent).	Concentration of erythrocytes before treatment. E_o (millions per cu.mm.).	Concentration of erythrocytes at peak of rise of reticulocytes. E_p (millions per cu.mm.).	Increase in erythrocyte concentration at peak of reticulocyte rise. $E_p - E_o$ (millions per cu.mm.).	Concentration of reticulocytes at peak of rise (observed). $E_p r$ (millions per cu.mm.).	Concentration of reticulocytes at peak of rise (estimated). $\frac{E_o r}{1-r}$ (millions per cu.mm.).
27	1.70	2.20	0.50	0.59	0.63
21	1.70	2.00	0.30	0.42	0.45
19	1.70	2.10	0.40	0.40	0.40
18	1.70	2.00	0.30	0.36	0.37
14	1.70	2.10	0.40	0.29	0.28
24	1.75	2.05	0.30	0.49	0.55
21	1.75	2.00	0.25	0.42	0.47
16	1.75	....	....	....	0.33
Average when E_o varied from 1.7 to 1.8					0.44
21	1.80	....	....	....	0.48
18	1.80	2.20	0.40	0.40	0.40
16	1.80	2.10	0.30	0.34	0.34
21	1.90	....	....	....	0.51
16	1.90	....	....	....	0.36
12	1.95	....	....	....	0.27
11	1.90	2.25	0.35	0.25	0.24
11	1.98	2.23	0.25	0.25	0.24
Average when E_o varied from 1.8 to 2.0					0.36
25	2.00	2.50	0.50	0.63	0.67
12	2.00	....	....	....	0.27
10	2.00	2.30	0.30	0.23	0.22
9	2.00	2.20	0.20	0.20	0.20
18	2.05	2.60	0.55	0.47	0.45
19	2.10	....	....	....	0.49
8	2.10	....	....	....	0.18
8	2.10	2.22	0.12	0.18	0.18
12	2.20	....	....	....	0.30
10	2.20	2.40	0.20	0.24	0.24
Average when E_o varied from 2.0 to 2.2					0.36
8	2.30	2.70	0.40	0.22	0.20
11	2.50	3.00	0.50	0.33	0.31
9	2.50	3.10	0.60	0.28	0.25
8	2.50	3.00	0.50	0.24	0.22
9	2.65	....	....	....	0.26
14	2.72	3.11	0.39	0.44	0.44
6	2.80	....	....	....	0.18
Average when E_o varied from 2.2 to 2.8					0.27
5	3.00	3.12	0.12	0.16	0.16
3	3.00	....	....	....	0.09
3	3.00	3.35	0.35	0.10	0.09
3	3.10	3.30	0.20	0.10	0.10
3	3.10	....	....	....	0.10
2	3.10	3.10	0.00	0.06	0.06
4	3.20	3.30	0.10	0.13	0.13
2	3.30	3.50	0.20	0.07	0.07
Average when E_o greater than 3.0					0.10

* The reticulocytes before treatment formed usually less than 3 per cent of the erythrocytes and rarely from 5 to 8 per cent.

relatively large amounts of the standardized liver extract were fed are more uniform and are recorded in Table I. In Fig. 1 the erythrocyte concentration of the patient at the beginning of treatment is plotted as abscissa, and the reticulocyte percentage as ordinate. This figure reveals the response of the reticulocytes in patients fed sufficient amounts of liver extract No. 343 to produce rapid improvement. It indicates an inverse relation between the percentage of reticulocytes in the blood at the peak of their rise and the concentration of erythrocytes before the beginning of the feeding. This relation may be employed in estimating the potency of the extracts.

The response of the reticulocytes not only yields information of value concerning the potency of material that is fed, but may aid in diagnosis when the erythrocytes are less than 3 million per cu.mm. of blood. If a patient with pernicious anemia is given untested material and there follows directly a reticulocyte response it indicates the presence of the active principle, although the remote possibility of a "spontaneous" reticulocyte rise at the precise time that one is expected from the substance administered, must not be overlooked. If no response of the young red blood cells occurs it is exceedingly probable that the substance fed is inert, because only very rarely will the reaction to potent material be absent in the blood of pernicious anemia with less than 3 million erythrocytes per cu.mm. of blood. Thus, failure to respond to potent material renders it exceedingly probable that the patient has not pernicious anemia. The presence or absence of the response does not determine the degree of potency of the material fed, but the maximal numbers of reticulocytes that appear and the rate of their increase gives useful information concerning this. If the reticulocytes at the peak of their rise fall below the level for comparable cases recorded in Fig. 1, the amount of material given was in all probability not a maximal dose. The daily administration of a quantity of potent material sufficient to yield a slight reticulocyte response may be insufficient to produce, within a few weeks, a distinct increase in the red blood cell level, or improvement in the health of the patient. Fig. 4 in the preceding paper illustrates this.

The course taken by the reticulocytes, after the feeding of liver, kidney or of liver extract, has been recorded elsewhere.[4, 3] In this place it should be noted that if the reticulocytes remain for an unusually long time close to their highest level the greatest percentage reached may fall considerably below that for the usual case at the same erythrocyte level. This circumstance is rare and occurred in but 3 of the 89 cases for which data are recorded in Table I and Fig. 1. When the total number of reticulocytes in the blood is compared in different cases, over a period of days, then those with sustained rises will be found to have had in their blood streams numbers comparable to those having a sharper peak for their

reticulocyte response. There are, thus, various other ways of recording and of studying the reaction of the reticulocytes.

The reticulocyte response is usually slight and may not be detected when the red blood cells are over 3 million per cu.mm. This probably is because the state of the marrow is then such that stimulating the growth of its red blood cells does not necessitate the delivery into the blood stream of many cells as immature as reticulocytes. The variations of the reticulocyte response in apparently similar cases and the influence of various amounts of extract are subsequently considered.

The Relation between the Erythrocyte Level and the Concentration of Reticulocytes. The response of the reticulocytes may be considered more rationally, provided their concentration rather than their percentage in the blood is calculated. The concentration of the reticulocytes in the blood at any time is equal to the product of the erythrocyte concentration times the percentage of reticulocytes (r). Although the erythrocyte concentration before the beginning of feeding (E_o) is generally well known as the result of measurements made over a period of days, the erythrocyte concentration at the peak of the reticulocyte rise has not always been measured. When it has, this quantity (designated E_p) is given in the third column of Table I, and in the fifth column is given the product $E_p r$. Methods of estimating the reticulocyte concentration when the erythrocyte concentration has not been measured at the same time, but shortly beforehand, are considered elsewhere.[3] These depend upon certain assumptions the nature of which need not again be described. Their justification depends upon the close agreement between the reticulocyte concentration calculated by means of the equation in the last column of Table I and the reticulocyte concentration measured in those cases in which the erythrocyte concentration was studied either on or near the day of the peak of the reticulocyte rise.

The calculation given in the last column in Table I assumes that the increase in the erythrocyte concentration during the first few days of feeding a potent extract is attributable to the increase in reticulocytes. The increase in erythrocyte concentration is given by the difference in the two red blood cell counts ($E_p - E_o$) and is recorded in the table. The large error in making red blood cell counts renders the difference between two such determinations very inaccurate. None the less, in the cases that have been most carefully studied, the agreement between the figures placed in the last three columns of the table is very satisfactory when the red blood cell level is low. Thus, the erythrocyte increase at the time of the peak of the reticulocyte rise is almost entirely to be accounted for in the cases with less than 2.5 million red blood cells per cu.mm. by reticulocytes. When the red blood cell count is relatively high, the entire increase in erythrocytes at the time of the peak of the reticulocyte rise, apparently, is not due to these young cells.

The percentage of reticulocytes in the blood at the peak of their rise varies more than does the reticulocyte concentration. The reticulocyte concentration shows a variation in the same direction as the reticulocyte percentage, however, when a sufficient amount of active principle has been given. It appears that the nearer the red blood cells approach normal numbers, the smaller will be the peak concentration of the reticulocytes. At red blood cell levels of over 3 million per cu.mm., the reticulocyte concentration is seldom more than 150,000. If the erythrocyte level is below 1 million per cu.mm. before the feeding of standardized extract derived from 400 or more gm. of liver, or 240 or more gm. of liver or kidney pulp, there will usually be in the blood over 500,000 reticulocytes per cu.mm. within a week after the beginning of treatment. In one critically studied case treated with one of the experimentally produced fractions, they reached over 880,000 per cu.mm. of blood.[3]

The averages have been taken from values in Table I of the maximal reticulocyte concentration reached when the erythrocyte concentration at the beginning of feeding was less than 1 million; when it varied from 1 to 1.2 million per cu.mm. and at other levels. Although there is a wide variation in the magnitude of the response, even of patients with similar red blood cell counts, and consuming the same amount of active material, there can be no doubt that the greater reticulocyte responses have been observed in cases with the lowest erythrocyte levels. These average results are plotted in Fig. 2 as ordinate, and the erythrocyte concentration, E_o, as abscissa. A straight line described by the equation $Er = 0.73 - 0.2\ E_o$ passes through these points, suggesting that the maximal reticulocyte concentration expressed in absolute numbers, is, on the average, inversely proportional to the erythrocyte concentration before the beginning of feeding; when adequate amounts of extract are given. Further, the above calculations indicate that the quantity E_o is essentially the same as that for the concentration of adult cells in the blood, at the time of the peak of the reticulocyte rise.

The Relation between the Amount of Active Principle and the Magnitude of the Reticulocyte Response. The conditions of the bone marrow upon which the reticulocyte response depends appear to be correlated more closely with the erythrocyte level than with any other factor that has thus far been brought under control, when large amounts of the active principle are administered. The symbols in Fig. 1 represent the different amounts of extract given daily. Different patients were fed the amounts derived respectively from 300, 400, 500 and 600 and more grams of liver. No outstanding difference in the response can be detected from an examination of Fig. 1. On the other hand, the administration daily of the amount of active principle extracted from 300 gm. of liver is sufficient to produce a very satisfactory response. The outstanding difference between the daily use of the extract from 300 or 600 gm. of liver tends

to affect the rate at which the response occurs, rather than its magnitude. On the average, if larger amounts of extract are fed, the reticulocytes and mature erythrocytes increase in the peripheral blood sooner and the rate of increase in erythrocyte concentration is also greater. Within certain limits the response thus tends to depend upon the total amount of extract rather than the daily dose. The number of cells formed in a given time in identical cases probably is directly related, up to a maximum, to the amount of active principle administered.

TABLE II.—RETICULOCYTE RESPONSE TO THE FEEDING OF SMALL AMOUNTS OF LIVER OR KIDNEY.

Percentage of reticulocytes at peak of rise. r.	Concentration of erythrocytes before treatment E_0 (millions per cu.mm.).	Concentration of reticulocytes at peak of rise $\frac{E_0 r}{1-r}$ (millions per cu.mm.).	Amount of liver or kidney fed per day (gm.).	Number of reticulocytes at peak of rise per gm. of liver or kidney. millions per cu.mm. per gm. per day.
7.0	1.25	0.094	60	0.0016
5.0	1.60	0.084	70	0.0012
9.5	0.80	0.084	75	0.0011
12.0	1.00	0.136	120	0.0011
9.0	1.35	0.134	120	0.0011
10.0	1.10	0.122	125	0.0010
9.0	1.25	0.124	125	0.0010
16.0	1.00	0.190	130	0.0015
8.0	2.25	0.196	140	0.0014
11.0	1.50	0.185	140	0.0013
15.0	0.90	0.159	150	0.0011
13.0	1.20	0.179	150	0.0012
12.0	1.20	0.164	150	0.0011
11.0	1.50	0.185	150	0.0012
13.0	1.50	0.224	150	0.0015
8.0	1.90	0.165	150	0.0011
18.0	1.20	0.263	150	0.0018
13.6	1.10	0.173	150	0.0012
13.0	1.65	0.247	160	0.0015
12.5	1.75	0.250	165	0.0015
9.6	2.55	0.271	175	0.0015
9.5	2.00	0.210	180	0.0012
18.0	1.40	0.307	180	0.0017
18.0	1.40	0.307	190	0.0016
Average				0.00131

In order to examine the relation between the amount of potent substance and the reticulocyte response without considering its rate, we must turn back to observations upon the feeding of small quantities of liver and kidney. Before considering the results recorded in Table II, it should be pointed out that when liver or kidney has been fed the amount given has been recorded as that of the cooked weight, or as the weight of the prepared raw pulp. As noted in a preceding paper[4] this amount varies considerably but may be considered as a rule to be about 25 per cent less than the

weight of the food as bought. Thus, 150 gm. of cooked liver, or raw liver pulp, were generally derived from about 200 gm. of whole liver. On the other hand, losses are experienced in the extraction of the active principle though these probably do not exceed 30 per cent in the standardized fraction. In comparing the results that have been recorded with this extract (Fig. 1) with those obtained with the prepared organs, it may be assumed that 300 gm. of the prepared liver was derived from 400 gm. of the organ. A comparable amount of the active principle would be contained in the standardized extract from between 400 and 500 gm., and would weigh but from 12 to 15 gm.

The red blood cell level of the cases fed small amounts of liver is recorded in the second column of Table II. These varied from 0.8 to 2.55 million per cu.mm of blood before the feeding of liver. The percentage of reticulocytes in the blood at the peak of their rise, given in the first column, varied from 5 to 18 per cent. These responses are smaller than practically any of those occurring at comparable erythrocyte levels, shown in Table I and Fig. 1, but the amounts of active material ingested were much smaller. Not only was the production of reticulocytes small, but it was for the most part slower under these circumstances. The ratio of the concentration of reticulocytes at the peak of their rise and the amount of liver or kidney fed per day, as recorded in the table, yields a constant which represents as a first approximation the number of reticulocytes that appeared at this time in the peripheral blood per gram of liver or kidney.*

These results are graphically presented in Fig. 3. When less than about 200 gm. of liver or kidney are fed, or amounts insufficient to produce the optimal responses recorded in Fig. 1, a simple relation appears to obtain between the amount of the active principle consumed and the number of reticulocytes formed when the red blood cells are less than 2.5 million per cu.mm. Indeed the relations revealed in Fig. 3 appear to yield a semiquantitative method of estimating the amount of active principle in an unknown fraction. Information concerning the influence of feeding small amounts of potent material has also been derived from the feeding of extracts.

If more of the active principle is consumed in cases with low red blood cell counts, there exists a somewhat different state of affairs than if a submaximal dose is given. When 180 gm. of liver or kidney are fed daily, not over approximately 250,000 reticulocytes per cu.mm. will be present at the peak of their rise. When 200 or more grams are given daily, or when the standardized extract is given, in amounts derived from 300 or more grams of liver daily, there is a considerable variation in the maximum concentration of reticulocytes per cubic millimeter of blood. When maximum

* This quantity should be diminished by about 25 per cent in order to yield the number of cells formed per gram of whole liver or kidney.

amounts are taken daily, the number of reticulocytes at the peak of their rise per gram of liver fed is nowhere nearly as constant as when smaller amounts are fed. Thus, instead of their being close to 0.00131 millions per cu.mm., their number varies widely in different cases from 0.0010 to 0.0040 per gm. of liver fed.

Under these circumstances, the reticulocyte response is partially correlated, as noted before (Figs. 1 and 2), with the red blood cell level, but there is a certain variation in the magnitude of the reticulocyte response of different patients given the same amount of active principle even when they have the same erythrocyte level.

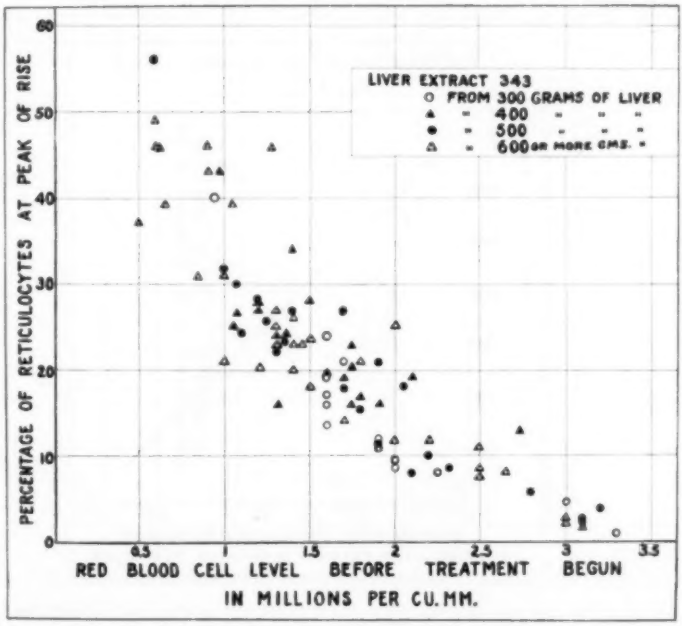

FIG. 1.—The response of the reticulocytes to the daily feeding of liver extract No. 343 in 89 cases of pernicious anemia.

This variability is probably to be attributed to the state of the bone marrow. In some instances there may be many primitive cells to be transformed, in others the bone marrow may not be sufficiently pathologic to allow more reticulocytes to enter the blood stream, even if more active principle were given. Thus, in some cases 200 gm. of liver, or the amount of standardized extract derived from 300 gm. of liver, is sufficient to cause the maximum reticulocyte response. In other cases a similar amount of active principle may not produce the greatest possible response. The daily consumption of extract derived from 300 gm. of liver may produce as many reticulocytes as that derived from 600 gm., but there are on the average

slightly fewer of these young red blood cells produced with the former than the latter amount.

One cannot predict any distinction in the number of reticulocytes to be expected in the blood when there are fed daily amounts of extract derived from 400 or more grams of liver. The daily administration of extract derived from 500 to 600 gm. of liver appears to be enough to create the maximal response in any case, although many patients apparently produce as many reticulocytes as possible when given a smaller amount. The variation in numbers of reticulocytes present at the peak of their rise following the administration of adequate amounts of extract in different cases with similar red

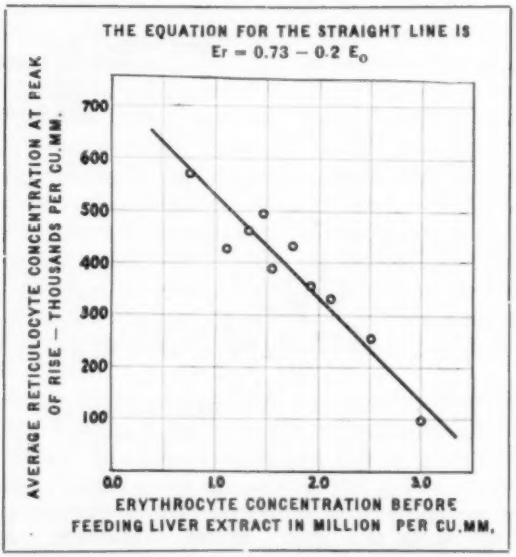

FIG. 2.—The average concentration of reticulocytes at the peak of their rise following treatment with liver extract No. 343 commenced at different erythrocyte levels. The equation for the straight line is Er = 0.73 − 0.2 E_0.

blood cell counts, as is given in Table I, reflects the variable state of the bone marrow. There may sometimes be many primitive cells to be transformed and sometimes relatively few. It is quite possible that the ease with which the cells can be transformed in the bone marrow is a factor in the response and that the threshold amount of extract to produce increases of reticulocytes in the blood varies. On the other hand active principle circulating in the blood stream may hasten the disappearance from newly formed erythrocytes of the reticular material. As a result, smaller reticulocyte concentrations might be observed in certain cases given larger amounts of extract, that in others. The detailed study of these secondary variations in

the reticulocyte response must await further study. Over and above them there remains the striking regularity and intensity of the reticulocyte response.

The Relation between the Amount of Active Principle and the Rate of the Reticulocyte Response. The rate at which the young red blood cells reach the peak of their rise is influenced in a measure by the amount of potent material given and the level of the erythrocytes. When the reticulocytes have reached their maximal numbers in uncomplicated cases later than the tenth day, which has seldom occurred, the amount of material given has usually been small, or the red blood-cell level above 2.4 million per cu.mm. Even so, similar small amounts may occasionally produce the peak of the reticulocyte rise about as soon as very large amounts. However,

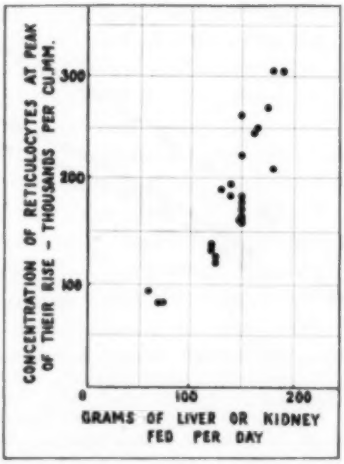

FIG. 3.—The reticulocyte response to the feeding of relatively small amounts of liver or kidney.

the average has been found to be eight and a half days for cases given daily about 150 gm. of prepared liver, or rather less than the amount of extract derived from 300 gm. of liver. In contrast, an average for cases given daily the extract from 600 or more grams of liver, shows the reticulocyte peak to have occurred on the seventh day, which is the same day as that on which the maximal percentage of reticulocytes occurred, on the average, in patients fed daily about 240 gm. of liver or kidney. The few cases that developed the peak of their reticulocyte rise as soon as the fifth day had distinctly low red blood cell counts.

The Relation between the Amount of Active Principle and the Erythrocyte Response. There is a direct relationship between the velocity at which the red blood cells increase and the amount of potent

material given, up to a maximum. Their rate of manufacture is slower when their initial count is above 2.5 million per cu.mm. This might be foretold from the reticulocyte response. When the reticulocyte response is obviously not maximal, or is delayed, the rate of erythrocyte increase is generally slow.

When the young red blood cells of a patient have apparently responded completely to the extract from 300 gm. of liver, the erythrocytes may rise more slowly than if twice as much potent material is given. On the other hand, some cases placed on the extract from 300 gm. of liver daily have increased their red blood cells as fast as the average case on extract from 600 gm. daily. This

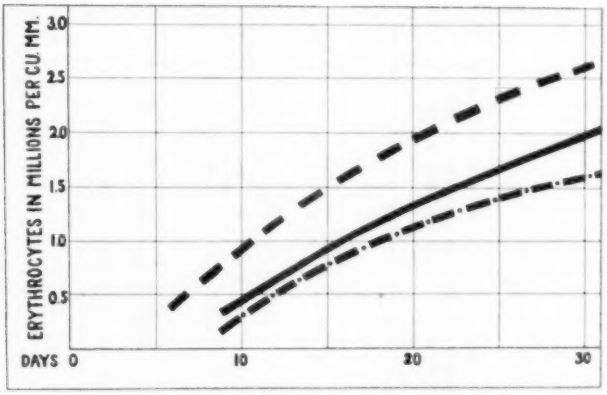

FIG. 4.—The average rate of erythrocyte increase in four groups of cases with less than 2 million red blood cells per cu.mm.

— — — — — Average for 24 cases fed daily with liver extract derived from 500 or 600 gm. of liver. No definite difference existed between the average rates of red blood cell rises when one or the other of those amounts were fed. This line also represents the average for 9 cases fed daily with about 240 gm. of prepared liver or kidney, that is, about 320 gm. as purchased.

——————— Average for 9 cases fed daily with liver extract in amounts approximately equivalent to liver extract No. 343 derived from 250+ gm. of liver.

—·—·—·—·— Average for 7 cases fed daily with about 150 gm. of prepared liver, that is, about 200 gm. as purchased.

variation may depend upon the same or similar conditions that influence the reticulocyte response when large amounts of effective material are given; namely, that the maximal effective dose varies for different cases. It is quite possible that a dose that just produces the maximal reticulocyte response is a little less for a given case than the amount required for the most rapid production of red blood corpuscles. Although different cases with similar levels of red blood cells may have reticulocyte responses of variable degrees to maximal doses of liver extract, figures at hand show that the red blood cells in such a group of patients may increase at about the same rate.

In all cases fed adequate amounts of potent fractions of liver for about ten days or longer, the red blood cells have with regularity increased promptly, so that within twenty-one days rarely less than 1.5 million and usually about 2 million per cu.mm., have been delivered into the blood stream. Sepsis and complications may delay the rate of the red blood cell rise, retard and decrease the response of the reticulocytes, yet in the presence of pneumonia maximal and prompt responses of the reticulocytes have occurred and pronounced rises in the total number of corpuscles. In 1 case, transfused over forty times, liver fraction produced in a month an increase of only 0.5 million corpuscles per cu.mm. A similar case has previously been referred to.[2] In two elderly patients with red blood cell counts of about 2.8 million per cu.mm. and very pronounced spinal-cord lesions, the response of the red blood cells to the feeding of liver fraction was relatively slight during the first few weeks. A few far-advanced cases died shortly after the treatment with fraction was begun, and before sufficient time had elapsed for the ingestion of enough material for its potent action. Death occurred from complications that had arisen prior to therapy.

The average rate at which the red blood cells increased in 105 patients fed liver or kidney, some of whom took very large and others very small amounts and whose red blood cells before treatment varied from 0.5 to 2.7 million per cu.mm., has heretofore been presented graphically.[2] The average increase in the red blood cells of these cases in about a month was 1.9 million per cu.mm. The cases formed an essentially consecutive series and some had complications that impeded blood formation. Fig. 4 illustrates the average rate at which the red blood cells may be expected to increase when uncomplicated cases with counts below 2 million per cu.mm. are given different amounts of liver or kidney or different amounts of potent fractions.

Table III contains the data upon which Fig. 4 is based and shows further the relationship between the average rate of red blood cell production and the numbers of reticulocytes at the peak of their rise. In comparing the absolute number of reticulocytes in the different groups of cases in Table III, one must take into consideration the initial level of the red blood corpuscles which is given in the table. The cases which yielded the average numbers in Fig. 4 and Table III were chosen because data on them were particularly complete. The facts at hand concerning many other cases indicate that the information given is representative of a much larger series. Inspection of the figure shows that whereas the feeding of about 150 gm. of liver a day caused the red blood cells to increase about 1.5 million per cu.mm. in thirty days, approximately 240 gm. caused a more rapid rise, so that about 2.5 million red blood cells per cu.mm. were produced in this same amount of time. The few cases fed daily over 240 gm. and up to 350 gm. of liver pulp had on the

average a slightly greater rate of increase of their red cells than the average for those patients who took 240 gm.

TABLE III.—RETICULOCYTE AND ERYTHROCYTE CONCENTRATIONS AFTER TREATMENT WITH DIFFERENT AMOUNTS OF LIVER, OR KIDNEY, OR LIVER EXTRACT.

Method of observation.	Days after treatment.	Sources of active principle effective in pernicious anemia.					
		Liver or kidney.		Liver extract derived from:			
		150 gm.* (7 cases).	240 gm.* (9 cases).	250 gm.† (9 cases).	400 gm. (5 cases).	500 gm. (12 cases).	600 gm. (12 cases).
		Concentration of red blood cells: millions per cu. mm.					
Average concentration of erythrocytes before treatment = E_0	0	1.52	1.38	1.35	1.48	1.29	1.10
Average concentration of reticulocytes at peak of rise (estimated) = $\frac{E_0 r}{1-r}$	7 to 8‡	0.19	0.43	0.37	0.38	0.47	0.49
(measured) = $E_p r$		0.21	0.44	0.35	0.41	0.46	0.50
Average increase in erythrocyte concentration = $E_{12}-E_0$	12	0.52	1.20	0.64	0.90	1.16	1.08
" $E_{21}-E_0$	21	1.16	1.92	1.35	1.65	1.91	2.05
" $E_{30}-E_0$	30	1.59	2.53	1.98	2.30	2.57	2.65
Minimal increase in erythrocyte concentration = $E_{30}-E_0$	30	1.20	2.10	1.60	1.70	2.10	2.30
Maximal increase in erythrocyte concentration = $E_{30}-E_0$	30	2.20	2.90	2.50	2.60	2.90	3.10
Average concentration of erythrocytes after thirty days of extract = E_{30}	30	3.11	3.91	3.33	3.78	3.88	3.72

* These weights refer to the prepared organs and represent approximately 200 and 320 gm. of original material.

† The cases recorded in this column were given weaker extract than 343 in such amounts that, though derived from 300 gm. liver, it was approximately equivalent to extract 343 derived from 250+ gm. of liver.

‡ The average peak day occurred sooner the more potent material was given: for liver, respectively after 8.57 and 7.00 days, and for the different amounts of extract after 8.43, 7.60, 7.09 and 7.01 days.

Sometimes cases with less than 2 million red blood cell corpuscles per cu.mm. of blood, fed daily extract from 500 or 600 gm. of liver,

have had their cells increased by 3 million per cu.mm. in a month, but on the average either of these amounts of extract has caused an increase of about 2.6 million cells per cu.mm. in this period of time. Cases treated daily with liver extract obtained from 800 to 1200 gm. of liver for the first six to fourteen days and then daily an amount from 600 gm., yield no definite evidence that these large amounts cause the manufacture of cells at a faster rate. No definite distinction in the number of cells produced during the first thirty days of therapy has been observed when the standardized extract derived from 400, 500 and 600 gm. of liver has been given daily to entirely comparable cases. There is perhaps a slightly greater rate of increase of the corpuscles, especially in the first ten days, when the larger amounts are given, and a statistical study of the maximum productions of cells further suggests that extract derived from 500 or 600 gm. of liver is slightly more efficacious than 400.

There is at hand little data concerning the rate of red blood corpuscle increase during a month in patients treated with an amount of extract No. 343 derived from 300 gm. of liver. Sometimes this amount has caused the corpuscles to increase as much as 2.7 million per cu.mm. in thirty days, but more often an increase of about 2 million per cu.mm. has occurred. The extract derived from 300 gm. of liver by a method that produced a less potent fraction than that now employed (equal approximately to that derived from 250 + gm. of 343) increased the red blood cells, on the average, by just under 2 million per cu.mm. in thirty days, in cases with initial counts below 2 million per cu.mm. As noted before, the greater the red blood cell count above 2.5 million per cu.mm. the less rapid is the red blood cell rise. When the standardized extract, derived from 400, 500 or 600 gm. of liver, has been fed daily to patients with initial counts between 2.5 and 3.1 million per cu.mm., the red blood cells have increased in a month sometimes a little over 2 million, but usually about 1.5 million per cu.mm.

The accumulated evidence indicates that the red blood cells continue to rise in an orderly manner when the daily feeding of suitable amounts of potent fraction is continued beyond thirty days. The exact rate of their increase after a month as a result of taking fraction cannot yet be determined, since until recently there has been little potent material available. In many instances as soon as the patient had improved distinctly and his red blood cells had increased 2 million per cu.mm., he was placed on liver or kidney, reserving the supply of fraction for individuals who were in a more serious condition. We have ourselves 28 patients under observation, who have been treated for more than two months and up to seven months with fractions of liver and who have eaten no liver or kidney. The red blood corpuscles in all these patients were over 4.4 million and averaged 4.9 million per cu.mm. two months after therapy was commenced. Counts over 4.2 million per cu.mm. have been main-

tained in all patients who have taken daily from two and a half to seven months not less than an amount of extract derived from 300 gm. of liver.

Treatment of Pernicious Anemia. The experience that has been gained in the treatment of pernicious anemia by means of liver and of fractions of liver has been formulated in semiquantitive terms in the preceding sections of this paper. Criteria have been established which on the one hand have facilitated the fractionation of liver and the standardization of an extract of known potency, and on the other hand have rendered it possible to follow the recovery of patients in whom the course of the disease was arrested at different erythrocyte levels and by the use of different amounts of the active principle.

Certain generalizations may be deduced from this experience which indicate that essentially all cases can be strikingly and promptly benefited. Thus, it may be recommended that a patient with a low red blood cell count be given daily, at first, the amount of liver extract derived from 500 or 600 gm. of liver, in order to insure rapid recovery from a critical condition. Less than this amount may produce an entirely satisfactory improvement in health. Certainly the extract derived from 300 or 400 gm. of liver produces striking improvement and such a daily dose may be entirely sufficient. In any case such amounts may be recommended as satisfactory, for patients in a fair state of health, especially if their count is 2 million or more per cu.mm. It has been our custom to reduce the daily dose to the amount of extract derived from 300 or 400 gm., of liver as the red blood cell count rose above 3 million per cu.mm. and to maintain this dose at least until the count was more than 4 million per cu.mm.

The necessity for prolonged continuation of liver therapy must be emphasized. Up to the present time the chief cause for patients with pernicious anemia to develop significant decreases in the level of their red blood cells, after they have once reached normal, following the eating of liver or kidney, has been the omission of these foods from their diet, or the ingestion of an inadequate amount.[2] It is probable that a suitable maintainance dose of liver extract will be found to vary for different patients. The further experience of many observers will unquestionably establish concrete information concerning dosage, particularly when the concentration of red blood cells is above 4.5 million per cu.mm. Numerous cases with high counts have been placed daily either upon the standard extract from 200 or 100 gm. of liver, and it appears that more than this latter amount is often a desirable quantity. It is important not to allow the dose to become too small to maintain at normal the red blood cell level. It is also desirable not to put an unnecessary strain upon the bone marrow. Red blood cell counts in the vicinity of 6 million per cu.mm. have occurred as a result of liver therapy.

Under these circumstances the amount of active principle administered should be curtailed. It is desirable that the blood of patients be examined from time to time, and the amount of active principle prescribed be dependent upon the state of the blood, and upon the symptoms or signs manifested by the patient. If neurological disorders appear to progress more of the active principle should be given. An infectious process may cause the red blood cell count to fall, or prevent its rise,[2] and under such circumstances maximal amounts of potent material should be fed.

A description of the rapid symptomatic improvement and gain in health of patients given fractions of liver would for the most part constitute a repetition of the observations of Minot and Murphy[1,2] upon the feeding of liver. The improvement which occurs with regularity is first noticeable as the reticulocytes start to rise. It has formerly been stated[2] that tongue symptoms had not returned in patients who took a well-balanced diet rich in liver. Since that statement was made, glossitis has been observed to occur mildly, but temporarily, in 3 patients apparently digesting a satisfactory amount of liver. This also took place in 1 patient after he had had with regularity liver fraction for three months. The results obtained with liver differed but slightly from those thus far noted with the standardized extract, or with the purest fraction that has been prepared,[3] of which but some tenths of a gram a day constitutes an adequate amount.

The clinical improvement of the group of patients given fractions of liver has apparently been more rapid than those given the whole liver. This has probably depended upon the greater ease with which larger amounts of the active principle have been administered, particularly to the very sick; even to those in a comatose condition. Very sick patients so treated have responded with extraordinary improvement. The powdered extract from as much as 600 gm. of liver is readily dissolved in 60 cc. of water, orange juice or any other acceptable vehicle and may be given as one or as several doses.

Although the rate of increase in the concentration of red blood cells often has been more rapid in patients upon fraction than in those given whole liver, the rate of hemoglobin formation on the average has appeared to be somewhat slower. As the rise of the hemoglobin concentration accompanies the increase to normal of the erythrocyte count following the feeding of large amounts of whole liver, the color index falls and often becomes less than 1.[2] Lower color indices have tended to occur at the time that the concentration of red blood cells approached normal in the groups of patients fed fractions of liver than in those fed whole liver. The hemoglobin concentration appears to have risen more slowly, particularly after an increase of about 25 per cent, in patients treated with extract than in those upon a similar diet that contained large amounts of whole liver. There are other substances in liver, among them iron, which facilitate hemoglobin

formation. The lack of these substances may become evident after some weeks of treatment when the critical stages of the disease are past and the specific substance deficient in pernicious anemia, and not obtained by the patient from his tissues or food, has been supplied. In order to discover what rôle other substances may play in blood regeneration in pernicious anemia, patients treated with fractions have been placed upon various diets, though these have never contained liver, kidney or other internal organs. So far only a few preliminary observations have been made but different diets during the first few weeks do not appear to alter in any important way the blood regeneration, or the patient's gain in health.

Two patients whose red blood cells and hemoglobin increased with extreme rapidity took practically only bread and water for the first twelve days that fraction was administered. Some patients have had diets with large, and others with small, amounts of fat, and foods rich in Vitamin A. Cases have been placed on diets composed particularly of concentrated carbohydrate foods and milk, sparing in fat, lacking in meat, poultry and eggs, and deficient in green vegetables and fruit. Such diets contain little iron and but little food of the sort that Whipple and Robscheit-Robbins[5] have shown promote hemoglobin formation in dogs with anemia due to chronic blood loss. Upon such diets hemoglobin apparently increases more slowly and possibly the red blood cells rose a little less rapidly after reaching 3 million per cu.mm., than in cases taking a well-balanced diet rich in red meat, fruit and green vegetables. Occasionally, even in cases fed liver and an adequate diet, the red blood cells upon reaching 3 million per cu.mm. have remained stationary for some days before a further increase was readily detected. This perhaps has been less noticeable in cases given an ordinary well-balanced diet than in patients fed little food of the sort that promotes hemoglobin formation. Sometimes upon adding fruit and red meat to the diet, the hemoglobin and the red blood cells have appeared to increase at a faster rate.

The rapid blood formation stimulated by the active principle effective in pernicious anemia may exhaust reserve supplies in the body and demand an adequate well-balanced diet for its unhampered continuation. The influence of various foodstuffs in pernicious anemia has been studied by Elders,[6] by Kœssler and his associates,[7] and others. Their observations should be extended and many aspects of diet must ultimately be considered. The rôle played by the regular occurrence of gastric achlorhydria and the disturbed digestive processes which together with an unbalanced or undesirable diet have often constituted the history of persons with the disease, must also be further studied. The experiences that have been considered indicate, however, that the specific substance that has been extracted from liver is the essential factor in the treatment of pernicious anemia, and that the rôle played by other foodstuffs in maintaining, or improving, health must be considered subsidiary.

The patients who have received liver extract have been given routinely no treatment other than an adequate well-balanced diet containing no liver or kidney; and when their red blood corpuscles were low, complete rest in bed. The diet for each patient has been prescribed for that individual, taking into consideration his weight and all aspects of the case. The importance of partaking of sufficient food to supply liberally, but not excessively, all requirements of the body has been emphasized and patients have been advised that their diet should contain liberal amounts of green vegetables and fruit and that excess of carbohydrate and free sugar be avoided. No unusual amount of protein is necessary but the patient must receive a sufficient supply of various sorts of protein to promote nutrition and stimulate digestive secretion. Fat in large amounts can hinder digestion and for various reasons may be undesirable in some cases, yet in others large amounts, or substances contained in fats, may be advantageous to help improve and maintain the patient's health.

The patient himself must not be overlooked in the treatment of his disease. Diluted hydrochloric acid, U. S. P., may aid in decreasing gastrointestinal symptoms and improving disordered gastric function. Transfusion of whole blood in desperately ill patients, exercise to retrain muscles and various symptomatic measures must be considered upon occasions.

No contraindication to the use of liver extract is known. Coincident with the appearance in the blood of many immature elements from the bone marrow, two cases have developed thrombosis. Such a disorder, and perhaps other undesirable consequences impossible to foretell, might arise from the rapid changes produced in the body by too large amounts of the potent material effective in pernicious anemia.

The chemical studies[3] upon the active principle indicate that the specific substance effective in pernicious anemia is present in liver, and even in the standardized liver extract, in very small amounts. Its action in the restoration of an essentially normal physiologic activity of the bone marrow is striking; permitting a rapid transformation and growth of the primitive cells. The hastened maturation of primitive red blood cells has not only been deduced from the observations that have been considered, but has been observed by Dr. Sabin[8] in chick embryo preparations.

Lack of red blood cells is but one feature of pernicious anemia. The gastrointestinal and central nervous system are involved, independently of the bone-marrow disorder or degree of anemia. The active principle also appears to cause a rapid disappearance of certain signs and symptoms, and to prevent the development or progress of others, referable to these systems, such as glossitis, diarrhea, and certain neural manifestations. Such effects are comparable to those that occur with deficiencies of internal secretions and that occur in pellagra, sprue, and vitamin-deficiency disease

when a suitable amount of a specific substance is supplied, lack of a source of which prevented normal physiologic function.

Summary. The experience gained from the treatment of over 160 cases of pernicious anemia by the daily feeding of adequate amounts of potent extracts of liver is recorded. Extracts containing the active principle effective in pernicious anemia, which acts specifically in small amounts, have simplified treatment. Treatment with potent extracts not only causes rapid blood regeneration, but appears to check the progress, or causes to vanish, certain signs and symptoms of the disease not directly related to the state of the blood or the blood-forming tissues.

A standardized extract of liver has been employed, which given daily in such amounts as are derived from 300 to 600 gm. of liver (from 9 to 18 gm. of the extract), has caused with regularity, prompt and striking improvement in the health of 89 patients. Similar results have been obtained in over 70 other cases treated with differently prepared fractions of liver. Serious complications may prevent improvement.

Both the percentage and absolute numbers of reticulocytes in the peripheral blood at the peak of their rise are related to the level of the red blood corpuscles at the time treatment is begun. These relations may be employed to help determine the potency of material fed a patient.

Up to the peak of the reticulocyte rise the increase in the concentration of total red blood corpuscles may be ascribed almost entirely to the production of reticulocytes when the red blood cells are less than 2.8 million per cu.mm.

In cases with over 3 million red blood cells per cu.mm., or in cases which have received daily maximal amounts of potent extract for over twelve days, the increase in the total concentration of red blood cells is dependent chiefly on the liberation from the bone marrow of mature corpuscles.

In pernicious anemia with less than 3 million red blood cells per cu.mm., the absence of a reticulocyte response renders it exceedingly probable that an impotent extract has been employed. On the other hand, if the extract given is known to be potent, and no distinct reticulocyte increase follows, it is very improbable that the patient has pernicious anemia, provided his red blood cells are below 3 million per cu.mm.

The number of reticulocytes that appear in the blood at the peak of their rise is roughly proportional to the amount of active principle ingested daily, provided submaximal amounts are fed to patients with less than 2.5 million red blood cells per cu.mm. When large amounts are given the reticulocytes are apt to appear sooner, and vary more in concentration, in different cases with the same erythrocyte level.

In some cases there are probably many primitive cells to be trans-

formed within the marrow and in others relatively few, so that in the latter more reticulocytes would not enter the blood stream even if more active principle were given. Standardized extract from 500 or 600 gm. of liver apparently is sufficient to produce a maximum response of young red blood cells in essentially all cases.

There is a direct relationship between the rate at which the red blood corpuscles increase and the amount of potent material fed, up to a maximum. On the average when liver extract derived from 500 to 600 gm. of liver has been fed daily to patients with less than 2 million red blood cells per cu.mm. of blood, it has increased the concentration of these cells about 2.5 million per cu.mm. in thirty days. After two months of adequate therapy with liver extract red blood cell counts in the vicinity of 5 million per cu.mm. are to be expected.

The patients treated with liver extract have been given an adequate well-balanced diet containing no liver or kidney. The striking and rapid symptomatic improvement has been comparable to that reported for cases treated with whole liver.

The active principle effective in pernicious anemia appears particularly to stimulate the formation of red blood cells. The return to normal of red blood corpuscles usually proceeds more rapidly than that of hemoglobin as the result of treatment with liver, with kidney, or with liver extract.

The hemoglobin increases perhaps more slowly in cases treated with liver extract and a diet poor in sources of iron, and in foods that accelerate hemoglobin regeneration, than when potent extracts are given and the diet is well balanced, and rich in such foods.

It is emphasized that the continued ingestion of some source of the active principle effective in pernicious anemia is necessary to prevent relapse in this disease.

Although different lots of liver extract No. 343 gave uniform results recorded above during the five-months period that it was being tested in the clinics collaborating with the Committee on Pernicious Anemia of the Harvard Medical School, a variation has since been detected from the standards deduced in this paper. It is anticipated that when a significant proportion of the active principle is lost in manufacture it will be corrected before the product is distributed.

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A CONSIDERATION OF LEUKEMIA, WITH ESPECIAL REFERENCE TO A SUBACUTE FORM.*

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In 1917 a splendid contribution to the study of acute myelogenous leukemia was published in a relatively obscure medical journal by Gorham.[1] Since then, although many case reports of acute leukemia have been published, accurate information regarding the condition is not widespread. The usual conception in the minds of the general profession is of the fulminating form, which has a spectacular clinical picture and runs a rapidly fatal course; but a large number of cases that might be termed subacute are of very insidious onset and run a gradual course. It is with regard to the diagnosis of this latter form that we particularly wish to speak. However, it is necessary first to say something of the acute form of the disease.

Acute leukemia is a fatal disease of unknown etiology, running a short course and characterized clinically by fever, hemorrhages and ulcerative changes of the mucous membranes and hematologically by the predominant presence of immature white cells in the blood.

It is important to establish a correct diagnosis of this fatal disease because it readily may be confused with other conditions, some of which are benign. For example, acute mononucleosis, which is always benign, might be mistaken for acute leukemia and a hopeless prognosis given; or a diagnostic error of the opposite kind might be made, such as a case of acute leukemia with rapid swelling of the neck glands, being confused with Ludwig's angina and an unnecessary incision made in the mass. So much confusion has

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arisen in regard to the proper diagnosis that in the paper aforementioned, by Gorham, five postulates were laid down to be fulfilled in order to properly record a case as acute myelogenous leukemia. These points were as follow: (1) An aleukemic or subleukemic stage; (2) an acute downward course with death ensuing within one to four months; (3) characteristic blood picture of myeloblasts and myelocytes with transition forms between the two; (4) typical course and histologic findings of the liver, spleen, bone marrow and lymph glands; (5) specific proof of myeloid elements by enzyme reactions. It is our belief that these postulates cannot always be satisfied, nor do we believe it is essential for clinical purposes that all of them be satisfied. Frequently it is manifestly impossible to observe a patient in the preliminary aleukemic or subleukemic stage and it is obvious, of course, that a postmortem cannot always be obtained in order to establish a correct diagnosis. Even the oxydase (enzyme) reaction in recent years has been questioned as an essential criterion in the diagnosis. The question of acute lymphatic leukemia also enters here and we must state at the outset that for our purposes we are not distinguishing between these two forms, since the course is similar, the clinical features much alike and the only differences being finer features in the blood picture and in the organs obtained at postmortem.

The form of leukemia to which we call particular attention runs a rather subacute course and has not been given a great deal of attention in medical writings. Usually there is an insidious onset with progressive loss of strength, increasing pallor, slight fever and perhaps fleeting pains in the muscles or joints. Frequently, a necrotic process in the mouth—around tooth sockets following the removal of teeth, or in the throat, smears of which show Vincent's organisms, may be the complaint that brings the patient to the physician. The general condition may seem so good that little attention is given to anything but the local lesion. Here exists the danger that physicians and dentists unfamiliar with the frequent association of acute leukemia and necrotic processes in the mouth may treat the lesion without thinking of the possibility of such an underlying condition. Weakness progresses and pallor increases, various forms of skin manifestations (leukemic or purpuric) may make their appearance and often hemorrhages occur from the mucous membranes or in the fundus of the eye. The temperature may increase; usually it is irregular and intermittent, and the patient takes on an appearance of sepsis. The spleen is usually palpable and becomes slightly larger during the course of illness, but never becomes as large or as firm as in chronic leukemia.* The

* Chronic leukemia quite often terminates with an acute exacerbation, and if the patient were seen for the first time during this terminal phase the impression might be gained that one was dealing with an acute leukemia, if there were no knowledge concerning the previous condition. The presence of a large hard spleen speaks for the chronic form of the disease.

superficial lymph nodes may or may not be enlarged. Treatment has no effect in saving life or in staying the progress of the disease. Death occurs at the end of several weeks or a few months.

Clinically, the process may resemble an infection such as typhoid fever, and patients are frequently admitted to the hospital with that tentative diagnosis. The similarity of the clinical features of this form of leukemia and subacute bacterial endocarditis is at times striking and the necessity for differential diagnosis may arise. The presence of a heart defect, fever and progressive anemia leads one to suspect bacterial endocarditis and a necrotic process in the mouth or throat, associated with fever and progressive anemia, should make one just as suspicious of subacute leukemia.

The important feature of this form of subacute leukemia, and the one upon which a diagnosis rests, is the result of careful blood study. So far as the hemoglobin and red cells are concerned, there is usually a progressive, severe anemia with marked changes in the red cells and the appearance of normoblasts, frequently in large numbers, especially just before death. In the beginning of the illness the white blood cells are often normal in number or frequently below normal, and may never go much above 8000 to 10,000 per c.mm. Usually, however, there is some leukocytosis in the course of the disease, and the white cells may go to 50,000 or higher. The important point to remember, however, is that leukopenia or normal leukocyte counts may prevail and that it is the study of the stained smear, and not the total count, that permits the diagnosis to be made. The characteristic cell has the appearance of *immaturity*, and that is the striking feature, difficult to define but once seen readily appreciated, that aids in establishing a diagnosis. It is usually a large mononuclear cell with basophilic, nongranular cytoplasm and a large nucleus, with fine chromatin network, containing several nucleoli. At first glance these cells appear to be large lymphocytes, which is the reason that these cases formerly were classed mostly as lymphatic leukemia. It is now thought that these cells are usually of myelogenous origin.

This characteristic cell is frequently present almost to the exclusion of other cells—certainly neutrophils and cells of the lymphocytic series are remarkably reduced in numbers. Depending on the stage and rapidity of the disease process, one quite often may see other cells of more mature development; in fact, transition forms from myeloblasts to myelocytes are usually to be found in the myelogenous variety of subacute leukemia. The controversy as to the origin of this cell, like the question of the etiology of this disease, we do not propose to discuss. It is sufficient for us to recognize its immaturity and appreciate its significance. Many names may have been used to designate this cell, but probably "myeloblast" is best adapted to signify the immature form found in myelogenous leukemia. In lymphatic leukemia one deals with

FIG. 1.—Case I. Characteristic, immature white cell found in acute and subacute forms of leukemia. Note the nongranular cytoplasm and the single, large nucleus containing a number of nucleoli.

FIG. 2.—Case I. The same cell (higher magnification), showing a positive oxydase reaction.

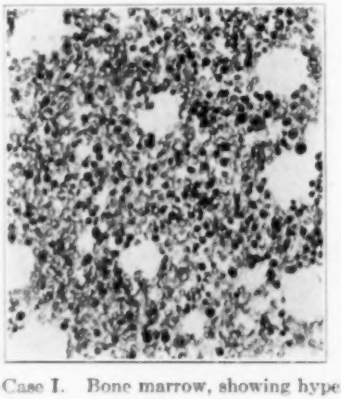

FIG. 3.—Case I. Bone marrow, showing hyperplasia.

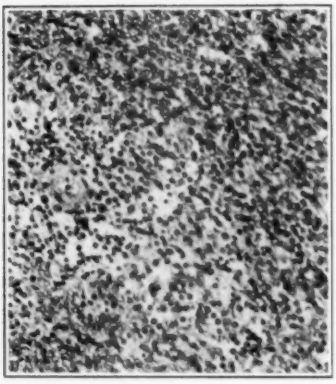

FIG. 4.—Case I. Spleen, showing myeloid change.

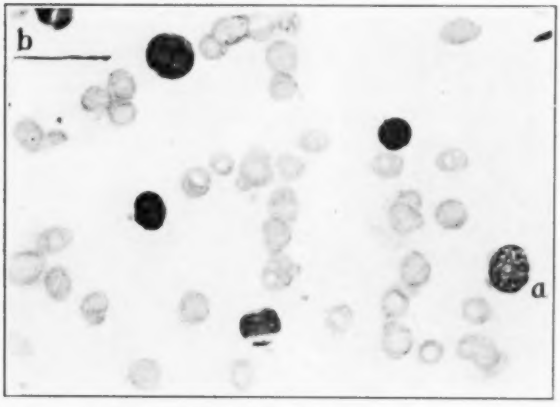

FIG. 5.—Case II. Immature white cells. Note chromatin arrangement in *a* and nucleoli in *b*.

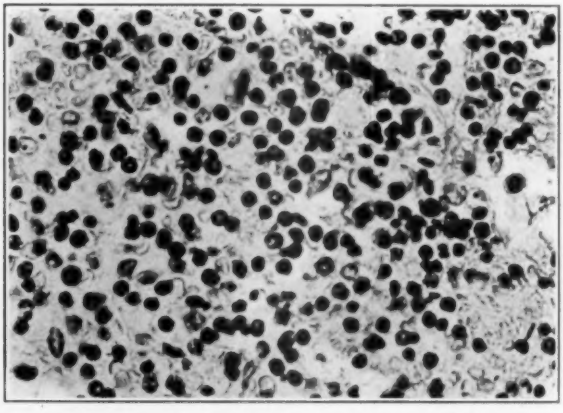

FIG. 6.—Case II. Marked cellular hyperplasia of bone marrow.

FIG. 7.—Case III. High magnification of three immature white cells and a polynuclear neutrophil. Note large single nucleus, nucleoli, fine chromatin network, vacuoles in nucleus and in the nongranular cytoplasm.

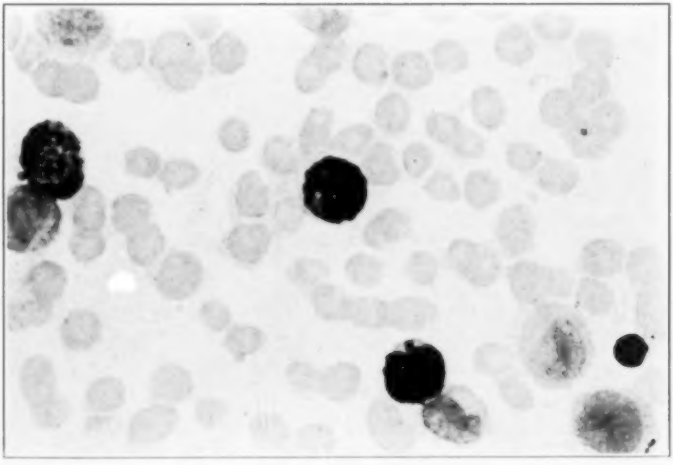

FIG. 8.—Case IV. Immature white cells, some of which show oxydase granules. (The stain has faded somewhat so that the cells not showing oxydase granules are pale.)

the lymphoblast, the morphologic features of which are so similar to the myeloblast that only expert hematologists attempt to distinguish between the two. Piney,[2] for example, says that the cytoplasm is the same in both cells, but that the nuclear characteristics are distinctive, in that the lymphoblast has a more distinct basichromatic stippling of the nucleus, and that the particles are coarser and are collected at the periphery to form a nuclear membrane. Formerly it was thought that the oxydase reaction would establish the origin of the cell without question, that is, that the cell giving a positive oxydase reaction must necessarily be of marrow origin and that the corollary was equally true; every white cell of marrow origin must give a positive oxydase reaction. While the oxydase reaction is undoubtedly helpful when positive, a negative reaction may be of little significance, since we have learned that very immature cells of marrow origin fail to give an oxydase reaction. A further fact of considerable importance established both by Piney[2] and Richter[3] is, that any cell giving a positive oxydase reaction will show granules if carefully stained by the usual methods.

The morbid anatomy of the subacute form of leukemia is distinctive and in obscure cases establishes the presence of the disease beyond controversy. In the myelogenous form there is myeloid metaplasia of the spleen, bone marrow, liver and lymph nodes and occasionally infiltration of such organs as the kidneys, lungs and heart. In the lymphatic form histologic changes differ, particularly in regard to the spleen in which one finds overgrowth of follicles at the expense of the pulp; the opposite of the myelogenous form.

Case Reports. One of the first cases of the subacute variety of leukemia to come to our attention was the following:

CASE I.—S. Y., a white woman, aged thirty-six years, a Russian Jewess, was admitted to the service of S. Solis-Cohen, at the Jefferson Hospital, November 27, 1922. She complained of generalized aches and pains of two weeks' duration. The family history was good. The personal history was negative. On admission to the hospital her temperature was 103° F.; pulse, 110; respirations, 28. She was a fairly well-nourished adult white female, of rather neurotic temperament. She did not seem to be particularly ill.

Physical examination showed a badly infected mouth, tongue furred, throat negative, no palpable lymph nodes in the neck. The heart was apparently normal. On the right side, posteriorly, below the angle of the scapula, crackling râles were heard on inspiration. Abdominal examination was negative. On the upper arms, and to a lesser extent on the thighs, were some small, elevated, reddened nodules somewhat sensitive to touch. Other than the above findings the physical examination was negative. It is noteworthy that the spleen was not palpable and there was no lymph-node enlargement. During the night of November 30 her left eye became very much swollen and engorged and the sight was impaired. The condition was pronounced "cellulitis." On December 15 the nodules on the arms and legs had almost entirely disappeared. The following day the left orbit was opened; nothing other than a little clotted blood was found, but not until the early part of January did the orbital cellulitis begin to subside.

On January 11 the edge of the spleen became palpable for the first time, but there was no generalized lymph-node enlargement. The spleen continued gradually to enlarge, and on February 13 it was noted three fingers' breadth below the costal border. On February 17 the patient had a severe epistaxis from the left nostril and coincident with this her general condition became rapidly worse. She died on February 20.

The striking feature was the result of the blood examinations. On November 27, the day of admission, her hemoglobin was 79 per cent; red blood cells, 3,970,000; white blood cells, 39,800; color index, 1; with a differential count which was first reported as 2 per cent of polymorphonuclear cells and 98 per cent mononuclear cells which varied in size from a small lymphocyte to a large mononuclear (Fig. 1). Two days later this count was repeated, with an almost identical result, but the Goodpasture stain was used and it was noted that the mononuclear cells gave a positive oxydase stain (Fig. 2). From then on to January 25 the blood count showed a rather rapid decline in hemoglobin and red blood cells, the white cells varying between 40,000 and 55,000. On January 25 the white cells began rapidly to increase, and by February 8 numbered 121,000. At that time the hemoglobin was 40 per cent and the red cells 2,000,000. A few normoblasts were found. The day before death the white cells dropped to 16,000 and coincident with this, a larger number of nucleated red cells appeared. Other laboratory examinations showed nothing of great importance. Two cultures of blood were reported sterile; the Wassermann was negative. The urine showed a faint trace of albumin and occasional hyalin casts. The temperature during the entire stay in the hospital continued very irregular, varying from normal to 102° F., the pulse in proportion and the respirations but little affected.

After death the bone marrow (Fig. 3) and the spleen (Fig. 4) were obtained. The bone marrow of the lower third of the femur was examined and was found to be red and hyperplastic. The spleen weighed 240 gm. Smears made from spleen substance and bone marrow showed cells of the same type as found in the blood, and histologic examination of the fixed tissue disclosed myeloid metaplasia.

Comment. Although this patient did not seem particularly ill on admission to the hospital, the steadily progressive downward course of the illness with the characteristic predominance of immature white cells in the blood smear did not leave the diagnosis in doubt for long. The point of consideration at that time was whether we were dealing with the process termed by Leube, leukanemia, partaking both of the characteristics of leukemia and pernicious anemia. Symmers[4] had just recently used this term in the publication of a case having such features. Piney[2] feels, as we did at that time, that such processes are simply leukemic with associated profound alterations of the erythrogenetic function.

Case II.—S. M., a Jewess, aged twenty-four years, was admitted to the medical service of S. Solis-Cohen at the Jefferson Hospital on August 23, 1926. Her chief complaint was weakness.

The family history was negative. She had always enjoyed good health; married at the age of eighteen years and had two children living and well. Five weeks before admission to the hospital she had developed a sore throat, but for several months previous to that had been feeling weak. The throat trouble progressed intermittently, and on August 2 her physician opened an "abscess" and after this she felt somewhat better.

Physical examination on admission to the hospital showed a rather pale, but fairly well-nourished girl. There was a necrotic process on the left tonsil and a few small postcervical nodes on the left side, but no general adenopathy. The edge of the spleen was just palpable beneath the costal margin, and the liver edge could be felt four fingers below the costal margin. There were no petechiæ. Examination of the eyegrounds showed minute hemorrhages and a diagnosis of neuroretinitis of anemia was made. Shortly after admission the left side of the face became swollen, but the sinuses were declared negative. The urine examination was negative. The blood Wassermann was negative. A smear from the necrotic process on the tonsil was positive for Vincent's organisms. During her stay in the hospital three blood transfusions were given without sustained benefit. The important feature of her examination was the blood count. On admission she had 6700 white blood cells, of which 76 per cent were mononuclears. During the following month the white blood cells gradually increased to 58,500, but later dropped to 19,000 and just before death to 3000. The hemoglobin averaged about 20 per cent and the red blood cells decreased from 1,780,000 to 880,000. The temperature was irregular, averaging about 101° F. and occasionally going to 103° F. The mononuclear cells gradually increased in proportion up to 95 per cent. The characteristic cell (Fig. 5) had a large nucleus with several nucleoli and basophilic vacuolated nongranular cytoplasm which failed to give an oxydase reaction. The patient died on October 3.

Permission was granted only to examine the bone marrow from the femur, which was hyperplastic (Fig. 6).

Comment. This case proved the necessity for a study of the stained blood smear in a patient presenting anemia, fever and a sore throat, because the total leukocyte count on admission was within normal limits and never rose to what is generally considered leukemic proportions. The fall of the total leukocyte count just before death is another point of importance and constitutes an evil prognostic omen.

Case III.—A. S., an Italian woman, aged thirty-seven years, was admitted to the service of S. Solis-Cohen at the Jefferson Hospital on March 8, 1926. She complained of a sore mouth, weakness and swelling of the legs. The family history was negative. She had measles and mumps as a child and also typhoid fever. She had ten pregnancies; six children living and well, and four miscarriages in the early months of pregnancy. She had been in good health until November, 1925, when her mouth became sore. About Christmas time she had diphtheria and was sick in bed for four weeks. Three weeks before admission her legs became swollen, and there was progressive weakness, chilliness and fever. On admission to the hospital the patient showed marked pallor, but seemed well nourished. The temperature was 102° F. There was necrosis of the tooth socket of the left lower bicuspid and a necrotic process on the right tonsil smears from which showed Vincent's organisms. There was no generalized adenopathy. The spleen could not be felt, but the liver edge was palpable three fingers below the costal margin. A week after admission to the hospital a small area of skin necrosis was seen on the abdomen in the right inguinal region. It was surrounded by a red zone. Blood Wassermann examination was negative. Blood counts were distinguished by a leukocytosis of 27,000, which mounted rapidly to 43,000 and then just before death dropped to 12,000. The majority of the cells were large mononuclears with several nucleoli and basophilic nongranular cytoplasm (Fig. 7).

Some of them gave a positive oxydase reaction. The patient died on March 21. A necropsy was not obtained.

CASE IV.—A. D., a Russian Jewess, aged seventeen years, was admitted to the Jefferson Hospital, service of S. Solis-Cohen, December 20, 1923. She complained of nausea, vomiting, loss of appetite and cough. The family history was of no importance. The only points of importance in the past history follow: In 1920 the patient had an operation on the nose and a tonsillectomy, after which she developed a pulmonary abscess, which ruptured into the pleural cavity. For this she was operated upon and drainage instituted. Gradual improvement took place, cough and expectoration lessened, and in the summer of 1923 had almost entirely disappeared. About six weeks before admission to the hospital she had an infection of Bartholin's gland, which was opened and drained; she made a good recovery.

Present Illness. About the end of October, 1923, she lost her appetite, vomited frequently and became very pale. In November she noted that the menses were more profuse than normal. About a month before admission she blew a little clot of blood from the left nostril. Physical examination on admission demonstrated a lesion in the lung at the right base, which gave signs of cavity formation. Abdominal examination was negative; neither the spleen nor the liver were palpable. There was no generalized adenopathy; the teeth and gums were in good condition. Temperature was 101° F.; pulse, 120; respirations, 30. She became rapidly worse in the hospital. On December 25 she had a profuse nosebleed and the following day bled from the gums; on December 28 she had hemorrhages into both retinæ, obliterating sight. On December 30 the cervical lymph nodes began to enlarge, and on January 5 she died. No necropsy was permitted.

The blood count on admission showed a hemoglobin of 45 per cent; red blood cells, 2,260,000; white blood cells, 42,000, of which 20 per cent were polymorphonuclears and 77 per cent were mononuclears. The hemoglobin and red cells rapidly fell and the white cells steadily increased so that by January 4 the total white count was 209,000 and the mononuclear cells made up 97 per cent of the total number. Of these 20 per cent gave an oxydase reaction (Fig. 8).

CASE V.—R. B., a white male, aged thirteen years, was admitted to the Jefferson Hospital on the service of T. McCrae, October 23, 1923. The history was obtained from the mother, who stated that the illness began about two weeks before admission, when she noticed that the boy was pale, had fever and complained of headache. The family history was negative. He had his tonsils and adenoids removed at the age of five years, and during his eighth year had measles, mumps, whooping cough and influenza.

Physical examination on admission showed a well-nourished boy who did not seem particularly ill. There was some pallor. The spleen was enlarged and rather firm but not tender. The liver was not felt and there was no general enlargement of the lymph nodes. The spleen continued to enlarge during his stay in the hospital, finally extending as far as the navel and the cervical nodes became slightly enlarged and somewhat tender. The course of the illness was progressively downward and he died, January 1, 1924.

The blood count on admission was: Hemoglobin, 45 per cent; red blood cells, 2,620,000; white blood cells, 121,000, of which the great majority were abnormal mononuclear cells which failed to give the oxydase reaction. Occasional normoblasts were seen. Following radium application to the spleen the white cell count dropped to 8200, but later rose to 205,800 and remained high until death occurred. No necropsy was obtained.

CASE VI.—E. U., female, aged fifty-one years, was admitted to the Jefferson Hospital under the care of E. J. Klopp on June 15, 1925. She complained of swelling and ulceration of the lips, mouth and throat and difficulty and pain on swallowing. The family history disclosed that the father died of tuberculosis at the age of forty-five years. The mother, an aged woman, has carcinoma of the breast. Otherwise the family history was negative.

The patient had always enjoyed good general health. She had typhoid fever at the age of thirty-one years and recurrent attacks of tonsillitis up to the age of thirty-four years.

The onset of the present illness was in January, 1925. This began with an attack of acute tonsillitis with swelling of the neck, difficulty and pain on swallowing and later swelling and ulceration of the gums, mouth and throat. There was a continued fever and the patient remained in bed until April. Early in April she had some small red, painful blotches on the legs and also a small abscess of the right vulva. Symptoms then ameliorated for a time. About ten days before admission there was a return of the swelling and ulceration of the mouth, so that the patient was unable to take nourishment.

On admission to the hospital, physical examination disclosed a well-nourished white female with slight jaundice, swollen and ulcerated lips, marked gingivitis, coated tongue and large tonsils with ulceration at the base of the right tonsil. There was some enlargement of the anterior cervical lymph nodes. The spleen and liver were palpable. There was a slight adenopathy in the groin and axillæ. The blood Wassermann and cultures were negative. No Vincent's organisms were found in the mouth. On June 15 the blood count showed: Hemoglobin, 55 per cent; red blood cells, 2,300,000; white blood cells, 20,000; giving a color index of 1.2 per cent; 65 per cent of the white cells were mononuclears with nongranular cytoplasm. These cells did not give a positive oxydase reaction. The red cells progressively decreased and the white cells increased up to 35,000 before death. The mononuclears increased in proportion up to 71 per cent. Death occurred on June 23, 1925, just six months after the beginning of the illness.

Differential Diagnosis. From a hematologic viewpoint a number of conditions are apt to be confused with the acute and subacute forms of leukemia. It is not our purpose to consider this question of differential diagnosis at length as this has recently been thoroughly done by Krumbhaar,[5] Piney[2] and others. It is sufficient to emphasize the necessity for repeated careful blood studies and a thorough consideration of the clinical course before making a diagnosis of a condition which carries a fatal prognosis. Among the most important processes which may have to be differentiated are acute mononucleosis, especially in its severer forms as reported by Davey and Whitby;[6] purpura hemorrhagica, such as a case reported by Farley;[7] leukemoid reaction to infections (any blood picture in which there is an increase in the number of immature cells) as in the case of whooping cough studied by us which showed a total white blood cell count of 80,000 with 52 per cent of mononuclear cells, and which was at first thought to be a case of acute leukemia. Other conditions which may possibly cause confusion in differential diagnosis are noninfective leukemoid reactions; an important form is that seen

accompanying the presence of secondary deposits of malignant tumors in bone marrow, agranulocytic angina, aplastic anemia and myeloma.

Of all these one must be especially on guard to differentiate acute mononucleosis and other benign infections with leukemoid reactions. The milder course of such processes, the absence of destructive changes of the red blood cells and the failure to consistently maintain a preponderance of immature white cells in the blood usually permits a differentiation to be made.

Conclusions. Acute leukemia generally is thought of as a fulminating process, with spectacular clinical picture, running a rapidly fatal course. However, a large number of cases, better termed subacute, have an insidious onset and run a gradual course of several months with fatal termination. Clinically they resemble typhoid fever or subacute bacterial endocarditis. The important symptoms are necrotic processes in the mouth or throat, fever and progressive anemia. The total leukocyte count may be normal or only slightly increased, but the study of the stained blood film shows the predominant presence of immature white cells. The oxydase reaction is sometimes helpful in determining whether these cells are lymphocytic or myelogenic in origin, although it is not practically important to distinguish the lymphatic and myelogenous forms of the disease.

Hematologic differentiation from acute mononucleosis and other benign leukemoid reactions is important and depends upon their milder clinical course, the absence of profound red blood cell changes and the failure of such processes to consistently maintain a preponderance of immature white cells in the blood.

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CLINICAL AND PATHOLOGIC DATA IN CASES EXHIBITING T-WAVE NEGATIVITY IN THE ELECTROCARDIOGRAMS.

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There has been considerable controversy and misunderstanding regarding the significance of established T-wave negativity in certain leads of the electrocardiogram.

Numerous publications[1 3 4 6 7 8 9 10] dealing with mortality statistics in these cases have given data that can only be interpreted as indicating the presence of myocardial disease resulting in a high and early incidence of cardiac death. It must be understood that the *T*-wave inversions under discussion are independent of the action of digitalis.

This investigation comprises 130 cases in which the electrocardiograms showed *T*-wave negativity other than in Lead III alone and in which necropsy was performed. Clinical data regarding these patients are presented in conjunction with the pathologic changes found at necropsy.

T-wave Negativity in Lead I. *Age and Sex Incidence.* There were 46 cases in which there was *T*-wave negativity in Lead I; 31 patients were males and 15 females, a ratio of 2 to 1. The majority of the cases occurred in the later decades of life, 42 cases (91 per cent) after the fortieth year and 32 cases (70 per cent) after the fiftieth year. (Table I.) Only 4 (9 per cent) occurred under the fortieth year and no cases were recorded in the first two decades.

TABLE I.—AGE INCIDENCE OF T-WAVE NEGATIVITY IN VARIOUS LEADS.

Decades.	Lead I.		Leads I and II.		Leads I, II and III.		Leads II and III.	
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
20 to 29	1	9	1	7	3	12	6	37
30 to 39	3		1		..		6	
Age 40								
40 to 49	10	91	7	93	7	88	7	63
50 to 59	14		9		9		7	
60 to 69	11	70	8	67	4	60	6	41
70 to 79	5		1		2			
80 to 89	2							

Clinical Types. Hypertensive heart disease occurred with greatest frequency in this group, there being 21 cases (40 per cent). Next in order of frequency was coronary disease, of which 13 cases (28 per cent) were recorded. Anginal attacks occurred in only 4 of these cases. The other clinical types were syphilitic aortitis, 5 cases (11 per cent); hyperfunctioning adenomatous goiter, 3 cases (7 per cent); exophthalmic goiter, 2 cases (4 per cent); aortic stenosis, 1 case (2 per cent); pernicious anemia, 1 case (2 per cent). (Table II.)

Associated Alterations in Cardiac Mechanism. Auricular fibrillation occurred in 10 cases, about one-fourth of the group. It occurred in 4 cases of hypertensive heart disease, 2 cases of coronary disease, 2 cases of hyperfunctioning adenomatous goiter, 1 case of syphilitic

aortitis and 1 case of aortic stenosis. Associated incomplete bundle-branch block was found in 7 cases (15 per cent), occurring in 3 instances in hypertensive heart disease, in 3 in coronary disease and in 1 in aortic stenosis. The last case was also complicated by auricular fibrillation. Ventricular tachycardia occurred only once, this being a case of hypertensive cardiac disease. One instance of nodal tachycardia was recorded in a case of hyperfunctioning adenomatous goiter. In 1 case of coronary disease there was auricular flutter and in 1 case of hypertensive heart disease complete heart block.

TABLE II.—CLINICAL TYPES ASSOCIATED WITH T-WAVE NEGATIVITY IN VARIOUS LEADS.

Types.	Lead I.		Leads I and II.		Leads I, II and III.		Leads II and III.		Totals.	
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
Hypertensive heart disease	21	46	15	56	13	52	5	16	54	41.4
Coronary disease	13	28	4	15	3	12	5	16	25	19.2
Syphilitic aortitis	5	11	2	7	1	4	1	3	9	6.9
Hyperfunctioning adenomatous goiter	3	7	1	4	..	..	3	9	7	5.3
Exophthalmic goiter	2	4	..	..	1	4	5	16	8	6.1
Aortic stenosis	1	2	3	11	2	8	4	13	10	7.6
Pernicious anemia	1	2	..	..	1	4	..	..	2	1.5
Adherent pericarditis	..	..	2	7	1	4	2	5	5	3.8
Subacute bacterial endocarditis	..	..	..	..	1	4	..	..	1	0.7
Postoperative heart failure	..	..	..	..	1	4	..	..	1	0.7
Metastatic carcinoma of pericardium	..	..	..	..	1	4	..	..	1	0.7
Mitral stenosis	..	..	..	..	..	..	4	13	4	3.0
Tuberculous pericarditis	..	..	..	..	..	..	1	3	1	0.7
Aortic insufficiency (rheumatic)	..	..	..	..	..	..	1	3	1	0.7
Pulmonary abscess	..	..	..	..	..	..	1	3	1	0.7
	46	..	27	..	25	..	32	..	130	

Antemortem Syndrome. The most common syndrome preceding death was congestive heart failure, which occurred in 25 cases (54 per cent). Auricular fibrillation was present in 8 of these cases. Hypertensive heart disease occurred with greatest frequency, having been present in 17 cases; coronary disease was present in 5 cases; aortic stenosis, syphilitic aortitis and hyperfunctioning adenomatous goiter, in 1 case each. There was anginal failure or death, occurring during the time of cardiac pain, in 8 cases (17 per cent); 4 of the 8 were cases of coronary disease, 3 of syphilitic aortitis and 1 of hypertensive heart disease. In the case of complete heart block death occurred during the time of a Stokes-Adams seizure. Death was attributable to causes other than cardiac in 12 cases (26 per cent).

These causes were miscellaneous, ranging from suicide to cancer of the prostate.

Pathologic Data. The weight of the heart was available in 36 cases; a definite increase in weight had occurred in most of the cases and the average was 582 gm. The lowest recorded weight was 282 gm., in a case of hyperfunctioning adenomatous goiter. The maximal weight of the heart was 1490 gm. and was found in a case of hypertensive heart disease. In 21 cases (58 per cent) the weight of the heart exceeded 500 gm., and in 19 (53 per cent) the weight ranged between 500 and 900 gm. (Table III.) As anticipated, the greatest weight of the heart was found in the group of cases of hypertension, in which the average was 700 gm. In the group of cases of coronary disease the average weight was considerably less (482 gm.), and this average was undoubtedly increased by the weights from some cases in which there was associated hypertension.

TABLE III.—SUMMARY OF WEIGHT OF THE HEART ASSOCIATED WITH T-WAVE NEGATIVITY IN VARIOUS LEADS.

Range of weight of heart, gm.	Lead I.	Leads I and II.	Leads I, II and III.	Leads II and III.
100 to 200	..	..	..	1
200 to 300	1	1	3	5
300 to 400	6	4	2	8
400 to 500	8	3	4	4
500 to 600	7	5	..	1
600 to 700	4	6	4	2
700 to 800	5	3	3	
800 to 900	3	1	1	2
900 to 1000	1	2		
1000 to 1500	1			

Some degree of coronary sclerosis was found in 39 cases (85 per cent). This was minimal in 8 cases, graded between 1 and 1+, and undoubtedly was insignificant insofar as it influenced the physiologic activity of the heart. In 31 cases the sclerosis was marked, ranging from 2 to 4+, and in 18 of these it was very marked, from 3 to 4+. Acute coronary closure with myocardial infarction occurred in 3 cases. In 2 cases the infarct was situated in the left ventricle and in 1 in the interventricular septum.

Disease of the aorta was found in every case. In 41 cases (89 per cent) varying degrees of arteriosclerosis and atheroma were demonstrated and, in the remainder, well-marked syphilitic disease. Minimal changes, graded 1 to 1+, occurred in 9 cases. In 37 cases (80 per cent) the changes were graded 2 to 4+.

T-wave Negativity in Leads I and II. *Age and Sex Incidence.* There were 27 cases of *T*-wave negativity in Leads I and II only; 15 of the patients were males and 12 were females. As in the foregoing group, the dominant age incidence was in the later decades; 25 cases (93 per cent) occurred after the fortieth year and 18 cases (67 per cent) after the fiftieth year (Table I); 2 cases (7 per cent)

occurred before the fortieth year and there were no cases in the first two decades.

Clinical Types. Hypertensive heart disease was the dominant clinical type in this group also, occurring in 15 cases (56 per cent). There were 4 cases (15 per cent) of coronary disease, 3 cases (11 per cent) of aortic stenosis, 2 cases (7 per cent) of syphilitic aortitis, 2 cases (7 per cent) of adherent pericarditis and 1 case (4 per cent) of hyperfunctioning adenomatous goiter. (Table II.)

Associated Alterations in Cardiac Mechanism. Incomplete bundle-branch block occurred twice, associated in 1 case with auricular fibrillation. One was a case of hypertensive heart disease, the other a case of coronary disease. No other alterations in mechanism were found in this group.

Antemortem Syndrome. Congestive heart failure was the syndrome preceding death in 18 cases (67 per cent). Auricular fibrillation was present in 8 of these. Hypertensive cardiac disease was the dominant clinical type, occurring in 11 cases. Aortic stenosis occurred in 3 cases, coronary disease in 2 and adherent pericarditis and hyperfunctioning adenomatous goiter in 1 case each. Anginal failure occurred in 3 cases (11 per cent); 2 of these were cases of syphilitic aortitis and 1 a case of coronary disease. In 3 cases (11 per cent) sudden death was accompanied neither by congestive nor anginal failure. All 3 were cases of hypertensive heart disease. No evidence of cerebral hemorrhage was found. Death unrelated to the heart occurred in 2 cases (7 per cent); it was caused by ulcerative colitis in a case of coronary disease and by mediastinal lymphosarcoma with invasion of the pericardium in another.

Pathologic Data.—Records of the weight of the heart were available in 25 cases and again definite increase in weight was the rule. The average weight of the heart for the group was 580 gm., almost identical to that in the foregoing group (582 gm.). The lowest recorded weight was 230 gm., occurring in a case of coronary disease, and the greatest weight was 960 gm., in a case of adherent pericarditis. The weight of the heart exceeded 500 gm. in 17 cases (68 per cent) and ranged between 500 and 800 gm. in 14 cases (56 per cent). (Table III.) The average weight of the heart in hypertensive cardiac disease was 605 gm. The average weight in coronary disease was 440 gm., again comparable to that in the previous group (482 gm.).

Coronary sclerosis in varying degrees was found in 21 cases (84 per cent). This finding was considered insignificant in 5 cases, graded 1 to 1+. It was marked in 16 cases, graded 2 to 4+, and extremely advanced in 10, graded 3 to 4+. Acute coronary obstruction with infarction of the left ventricle occurred in 1 case. In another case the right coronary artery was almost completely occluded by atherosclerosis.

Aortic disease was present in 23 cases (85 per cent). Atheroma or arteriosclerosis occurred in 21 cases and syphilitic disease in 2.

In 1 case of syphilitic aortitis almost complete atresia of the coronary orifices had taken place. Involvement of the aorta was slight in 5 cases and marked in 16 cases, graded 2 to 4+.

T-wave Negativity in Leads I, II and III. There were 25 cases in which *T*-wave negativity occurred in Leads I, II and III; 19 of the patients were males and 6 were females, a ratio of 3 to 1. The greatest incidence in this group also occurred after the fortieth year, 22 cases (88 per cent) being recorded. There were 15 cases (60 per cent) after the fiftieth year. In only 3 cases (12 per cent) was the patient under forty years, and there were no cases in the first two decades. (Table I.)

Clinical Types. This group was composed of a more miscellaneous collection of clinical types. Hypertensive heart disease again was most common, with 13 cases (52 per cent). Coronary disease occurred in 3 cases (12 per cent) and aortic stenosis in 2 (8 per cent) and there was 1 case (4 per cent) each of syphilitic aortitis, exophthalmic goiter, pernicious anemia, subacute bacterial endocarditis (mitral insufficiency), adherent pericarditis and metastatic carcinoma extensively involving the pericardium. (Table II.)

Associated Alterations in Cardiac Mechanism. Auricular fibrillation was present in 6 cases (24 per cent). It occurred in 5 cases of hypertensive heart disease and in 1 of aortic stenosis. Incomplete bundle-branch block was found in 3 cases of hypertensive heart disease (12 per cent).

Antemortem Syndrome. Congestive heart failure, the syndrome preceding death, occurred in 12 cases (48 per cent). Auricular fibrillation was present in 4 cases. Hypertensive heart disease occurred in 9 cases; aortic stenosis, adherent pericarditis and postoperative cardiac failure in 1 case each. Death with anginal failure occurred in 4 cases, comprising 2 cases of coronary disease, 1 of syphilitic aortitis and 1 of hypertensive heart disease. Death was due to causes not directly related to the heart in 9 cases (36 per cent). The causes were miscellaneous, ranging from pneumonia to uremia.

Pathologic Data. The weight of the heart in 21 cases was recorded, the average weight, 520 gm., being quite comparable to that of the other groups. The greatest recorded weight, 848 gm., occurred in a case of hypertensive heart disease; the lowest weight, 232 gm., in the case of subacute bacterial endocarditis. In 12 cases (48 per cent) the weight of the heart ranged between 500 and 900 gm. (Table III.) The average weight of the heart in the cases of hypertension was 632 gm.; in the cases of coronary disease it was 406 gm.

Sclerosis of the coronary arteries was present in 23 cases (92 per cent). The involvement was insignificant in 10 cases, graded 1 to 1+; in 13 cases (56 per cent) the sclerosis was marked, ranging from 2 to 4+, and in 7 (30 per cent) extremely marked, graded 3 to 4+. Acute coronary occlusion with infarction of the left ventricle occurred in 2 cases.

Disease of the aorta occurred in all but 1 case (96 per cent). Aortic sclerosis or atheroma occurred in 21 cases, and in 1 case syphilitic aortitis was present. The involvement was minimal in 7 cases, graded 1 to 1+, and marked in 17 cases, graded 2 to 4+.

T-wave Negativity in Leads II and III. *Age and Sex Incidence.* There were 32 cases in which there was *T*-wave negativity in Leads II and III only; 13 of the patients were males and 19 were females; in this group only were there more females than males. The greatest incidence occurred after the fortieth year, 20 cases (63 per cent). There were no cases in the first or the second decade. (Table I.)

Clinical Types. The clinical types in this group were miscellaneous, but showed a more uniform distribution. There was an equal number of cases of hypertensive heart disease, coronary disease and exophthalmic goiter, 5 cases of each (16 per cent). Aortic stenosis and mitral stenosis occurred in 4 cases each (13 per cent). Hyperfunctioning adenomatous goiter occurred in 3 cases (9 per cent), adherent pericarditis in 2 cases (5 per cent) and syphilitic aortitis, tuberculous pericarditis, rheumatic aortic insufficiency and pulmonary abscess in 1 case each. (Table II.)

Associated Alterations in Cardiac Mechanism. Auricular fibrillation was present in 9 cases (28 per cent). These comprised 3 cases of mitral stenosis, 2 cases of exophthalmic goiter, 2 cases of hyperfunctioning adenomatous goiter and 1 case each of coronary disease and aortic stenosis.

Antemortem Syndrome. In 16 cases (50 per cent) congestive heart failure was the antemortem syndrome. There were 4 cases of aortic stenosis, 4 of mitral stenosis, 4 of exophthalmic goiter and 1 case each of coronary disease, hyperfunctioning adenomatous goiter, hypertensive heart disease and syphilitic aortitis. There was only 1 instance (3 per cent) of anginal failure occurring in a case of coronary disease with acute obstruction. In 13 cases (40 per cent) death resulted from causes unrelated to the heart.

Pathologic Data. The weight of the heart was recorded in 23 cases. The lowest weight, 195 gm., occurred in a case of pulmonary abscess and the greatest weight, 862 gm., in a case of aortic stenosis. The average weight of the heart for the group was 416 gm., considerably less than the average for the other groups. The weight ranged between 500 and 900 gm. in only 5 cases (22 per cent). (Table III.)

Coronary sclerosis occurred in 22 cases (69 per cent). Involvement was minimal in 15 cases, graded 1 to 1+; marked in 7 cases, graded 2 to 4+, and extremely marked in 2 cases, graded 3 to 4+. Acute coronary closure with infarction of the left ventricle occurred in 2 cases.

Aortic disease occurred in 29 cases (91 per cent). The involvement consisted of sclerosis or atheroma in 28 cases, while in the other case there was well-marked syphilitic disease.

Discussion. It is apparent from the miscellaneous forms of cardiac disease represented in this study that *T*-wave negativity is not associated with a specific pathologic lesion of the heart muscle. However, two striking features are apparent: (1) The frequency of marked cardiac hypertrophy (500 gm. or more) occurring in 55 cases (42 per cent); (2) the prevalence of coronary disease of significant degree, graded 2 to 4+, occurring in 52 cases (40 per cent). While it is not possible to draw definite conclusions regarding this relationship, the high incidence of these two factors is very suggestive. It is not beyond conjecture that either marked cardiac hypertrophy or coronary disease, or both, are capable of producing alterations in the state of excitation of the ventricles and of influencing the refractory period.

It is important to analyze more carefully the cases in which there was neither marked cardiac hypertrophy nor significant coronary disease (23 cases, 18 per cent). In this group were 3 cases of pernicious anemia with marked anemia. The occurrence of the anginal syndrome in pernicious anemia, presumably the result of myocardial anoxemia, has been described by various observers.[5,11] Fahr and Ronzone, in their study of pernicious anemia, have shown that the coronary circulation is taxed to the limit and is comparable to that during strenuous work. It is possible that in certain cases of marked anemia a disturbance in circulation may occur sufficient to produce a condition similar to that existing in actual coronary disease.

In 12 cases there was exophthalmic goiter or hyperfunctioning adenomatous goiter. While I have found that alterations in cardiac mechanism other than auricular fibrillation and flutter are unusual in these cases, it is not impossible to conceive of myocardial injury in certain cases of a degree to give rise to other electrocardiographic variations.

In 1 case of syphilitic aortitis almost complete atresia of the coronary orifices occurred, giving rise to a condition identical to advanced coronary disease. In 2 cases adherent pericarditis was found, although in neither case was cardiac hypertrophy marked. It is uncertain whether there was sufficient interference with cardiac action to explain the abnormal tracings. The other cases comprised subacute bacterial endocarditis, postoperative failure, aortic stenosis with only moderate cardiac hypertrophy, mitral stenosis with moderate cardiac hypertrophy and pulmonary abscess. This group is puzzling and invites further study.

Summary. This study comprises 130 cases in which the electrocardiograms showed *T*-wave negativity (other than in Lead III alone) and in which necropsy was performed. An attempt is made to correlate the clinical features and the pathologic findings.

T-wave negativity in Lead I occurred in 46 cases, *T*-wave negativity in Leads I and II in 27 cases, *T*-wave negativity in Leads I, II and III in 25 cases and *T*-wave negativity in Leads II and III in 32 cases.

There were 78 males and 52 females in the entire group, a ratio of 3 to 2. The cases occurred dominantly after the fortieth year of life, 109 such cases (84 per cent) being recorded. There were no cases in the first or second decade.

The clinical types of cardiac disease were numerous, but hypertensive cardiac disease (54 cases, 42 per cent) and coronary disease (25 cases, 19 per cent) occurred with greatest frequency. Significant sclerosis of the coronary arteries was demonstrated at necropsy in 52 cases (40 per cent).

In 55 cases (42 per cent) the weight of the heart exceeded 500 gm.

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RHEUMATIC FEVER.

I. Observations Bearing on the Specificity of Streptococcus Cardioarthritidis in Rheumatic Fever and Sydenham's Chorea.

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(From the Special Rheumatic Fever Wards and the Laboratories of the Philadelphia General Hospital.)

In January, 1927,[1] attention was directed to a streptococcus which had been isolated from cultures of the blood and of the pharyngeal exudate of patients suffering from rheumatic fever. This

microörganism was designated Streptococcus cardioarthritidis and described as a new species on the basis of its distinctive cultural and immunological characters. The organism differs in its cultural characters from members of the Streptococcus viridans group and from the hemolytic streptococci in its failure to produce any obvious change in the medium adjacent to its colony, when grown on the surface of agar medium containing blood. It thus falls into a little studied subgroup of streptococci variously spoken of as nonhemolytic anhemolytic or indifferent streptococci. Other outstanding characters were shown to be the remarkable constancy of its fermentation reactions in media containing different test carbohydrates—particularly its ability to ferment inulin—and the ease of the identification of the newly isolated strains by means of a monovalent immune serum in the agglutination reaction. Extended experience[2] with a large number of strains of this microörganism has further emphasized the constancy of these distinctive characters.

A monovalent antiserum was prepared from a strain of Streptococcus cardioarthritidis and used in the treatment of patients suffering from rheumatic fever or chorea. The observations on a small number of patients treated with the antiserum were presented as a preliminary report of the effects of such treatment.[1] The microörganism was also shown to be capable of producing lesions of the heart, and joint structures when inoculated into rabbits.

Since this first report appeared, our observations of the Streptococcus cardioarthritidis and its biologic products in their relation to rheumatic fever have accumulated. It therefore seems best at this time to present a general outline of the nature of the significant observations, in an effort to avoid the delay necessarily occasioned by preparation and publication of several more detailed reports which will shortly appear in the more special journals. The work thus to be presented has been produced with the aid of the combined efforts of the various members of the staff of the Pathological Laboratory of the Philadelphia General Hospital, as well as that of volunteer workers associated in the work. Naturally in reviewing the developments arising from the combined efforts of an organized group concentrated on a problem presenting so many phases, it is not possible within the scope of one communication to present all pertinent data. The attempt is made, however, to present illustrative examples of the more outstanding features discussed.

The clinical material for the study was rendered available under favorable conditions, through the generous action of the Medical Staff and Medical Director of the Philadelphia General Hospital in providing a special rheumatic-fever service consisting of 2 eight-bed wards. These wards were especially equipped and provided with an efficient personnel for the care and treatment of the patients under observation. This report is based on a study of 232 patients, 137 of whom have been observed in the special wards.

TABLE I.—RHEUMATIC FEVER, CHOREA AND CHRONIC ARTHRITIS TREATED WITH ANTISERUM AND VACCINE OF STREPTOCOCCUS CARDIOARTHRITIDIS.

Diagnosis.	Number of cases.	Number treated with serum.	Number treated with vaccine alone.	Number receiving combined serum and vaccine treatment.	Predominating immediate results.[4]	Condition on last observation.[4]	Follow-up observations.	Remarks.
Acute rheumatic fever (first attack)	8 (Pericarditis, 2)	8	0	6	7 V.M.I.* 1 M.I.	6 C.D.S. 2 V.M.I.	2 D.F.O. 6 A.P.O. 286.1 days	One case of pericarditis relapsed twenty-nine days after administration of horse serum, and was then treated with bovine serum with good results.
Acute rheumatic fever (recurrent)[3]	64 (Pericarditis, 17)	61	3	52	42 V.M.I. 12 M.I. 10 N.I.	17 C.D.S. 35 V.M.I. 4 I. 8 D.	9 D.F.O. 8 D. 47 A.P.O. 239.3 days	Two relapses; 2 patients readmitted with cardiac decompensation; 3 deaths of patients on whom the lot "toxic serum" was used (see text); 2 cases moribund when treated and died within forty-eight hours; 1 cardiac failure (death) in a case of adhesive pericarditis; 1 sudden cardiac death in late serum disease in case of pericarditis and pneumonia; 1 patient with adhesive pericarditis and serious valvular disease died eleven months after serum treatment.
Sydenham's chorea	25	24	1	21	23 C.D.S. 1 V.M.I. 1 N.I.[2]	23 C.D.S. 2 M.I.	6 D.F.O. 19 A.P.O. 220.6 days	Two of 19 cases observed after leaving hospital showed mild recurrence while under vaccine treatment; reduction of vaccine dosage was followed by prompt disappearance of symptoms.
Chronic arthritis	40 (Atrophic, 27) (Hypertrophic, 9) (Unclassified, 4)	40	0[1]	32	5 C.D.S. 7 V.M.I. 14 M.I. 11 I. 3 N.I.	3 C.D.S. 6 V.M.I. 15 M.I. 11 I. 5 N.I.	6 D.F.O. 2 D. 32 A.P.O. 185.7 days	One died of pulmonary tuberculosis; 1 suicide.

* Key to abbreviations: C.D.S., complete disappearance of symptoms; V.M.I., very much improved; M.I., much improved; I., improved; N.I., not improved; D.F.O., disappearance from observation; A.P.O., average period of observation; D., died.

[1] Other patients treated with vaccine alone are not included in this tabulation.

[2] This patient received serum of the one lot referred to as "toxic serum" (see text).

[3] This tabulation includes for the most part cases treated with unconcentrated antiserum during the period of the development of the antiserum. It thus fails to reflect the results being obtained with the more potent concentrated antiserum.

[4] The estimates under "Predominating Immediate Results" and "Condition on Last Observation" take into consideration the cardiac symptoms. The acute arthritis, fever and other manifestations of the acute illness have subsided regularly where improvement is indicated, but these alone are not regarded as criteria on which the estimates are made.

The observations on the use of these products in the treatment of the rheumatic diseases have extended over little more than a year. It is obviously impossible at this time, therefore, to present statistical data bearing on the question of the permanency of the results obtained. A few disastrous results were obtained early with one lot of serum and a few relapses were observed early in this period. In an effort to present the facts available, and to give some idea, even though an approximate one, of the clinical results obtained, Table I has been compiled. It is further to be emphasized that this work has been in the strictest sense pioneering, in that there was everything to be learned in regard to both the preparation and the application of the antiserum and the vaccine. The antiserum under development had to be used in rather small lots at first. The serum of the different lots differed in antibody content, thus adding to the difficulties in estimating dosage. No practical measure of the effective antibody concentration of the serum has as yet been developed.

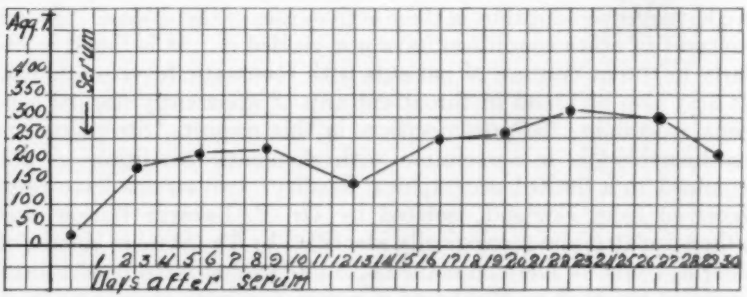
In the employment of the vaccines, continued difficulties arose from overdosage. It has required more than a year of experience to arrive at the extremely small dosage of the soluble products of the microörganism now employed. Questions both of underdosage of the antiserum and of overdosage of vaccines enter into any tabulation prepared at this time as factors militating against the results appearing in a statistical presentation.

Association of Streptococcus Cardioarthritidis with Rheumatic Fever. Streptococcus cardioarthritidis was in the first instance isolated in blood culture of a patient with rheumatic fever. While it is seldom recoverable from the blood in rheumatic-fever patients, we have recovered it thus in three active cases of this disease. Blood cultures in other conditions have not yielded it. It is found regularly in throat cultures of patients with rheumatic fever or chorea. It may also be found in throat cultures of apparently normal persons, resembling the pneumococcus in this respect. Streptococcus cardioarthritidis in association with rheumatic conditions is not confined to a limited geographical locality—two strains have been received from England, isolated by Dr. P. Lazarus Barlow and others isolated and serologically identified by Dr. Stanley Harris, of Beirut, Syria.[3] The nonmethemoglobin-forming streptococci more recently reported by Birkhaug[4] in association with rheumatic fever very likely include strains of Streptococcus cardioarthritidis.

Experimental Lesions. Lesions in animals following inoculations of streptococci have been demonstrated by many different workers.[5] There have always been differences of opinions in regard to the similarity of such lesions to the lesions of rheumatic fever. Mention of those produced by Streptococcus cardioarthritidis is made chiefly for the purpose of recording the fact that such lesions may be produced in animals. The strain specificity of this streptococcus and

its intimate association with the rheumatic diseases should provide sufficient stimulus for a more general interest in the experimental lesions of this organism. Streptococcus cardioarthritidis when inoculated into animals produces lesions in the myocardium, pericardium and cardiac valves; in the joints, their bursa or within the tendon sheaths; and in the central nervous system. The minute study of these lesions suggests some points of similarity to the spontaneous lesions of rheumatic fever. The lesions have been observed in rabbits and in horses.[6]

The lesions of the myocardium are perhaps the most significant. They seem to be simple of explanation. First there appears a destruction of the muscle fibers followed by the infiltration of cells, chiefly of the mononuclear variety, including large endothelioid cells, plasma cells, small round cells, and also occasionally polymorphonuclears and large multinuclear giant cells. The first and last-mentioned cells stain in the same manner with pyronin-methyl green as do the cells of the nodules of Aschoff. There appears also a remarkable proliferation of endothelium. This in the smaller bloodvessels frequently leads to complete occlusion of their lumina. It is possible that this latter lesion represents a fundamental one in such experimental infections, since occlusion of small bloodvessels may lead to microscopic areas of ischemic infarction, especially in those organs where end-arteries exist. The experimental infections with Streptococcus cardioarthritidis tend to chronicity in those animals which survive the acute stage closely following the inoculation. This is an uncommon experience with other experimental streptococcus infections in animals.

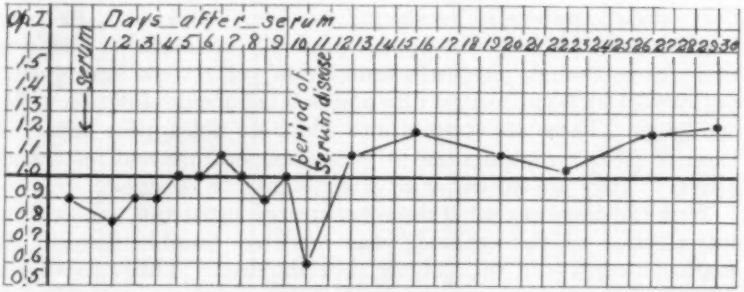


GRAPH I.—Composite graph of the agglutinin titer of 10 cases of acute rheumatic fever treated with antiserum.

Immune Bodies in the Serum of Patients with Rheumatic Fever. Early in the attack of acute rheumatic fever, agglutinins for Streptococcus cardioarthritidis are absent, or of low titer in the patient's blood serum. They increase during the course of the disease, but seem to disappear rather early following recovery. Graph I presents a composite curve of the titer of agglutinins in the sera of 10

patients with acute rheumatic fever covering a period of thirty days during which time semiweekly determinations of the titer of agglutinins were made. A gradual rise of titer is noted.

The opsonins[7] for Streptococcus cardioarthritidis in the patient's serum are low in amount during the acute stage of the disease, whether in the primary or in recurrent attacks. They rise during the favorable course of the disease, regardless of the mode of treatment, and persist at an elevated level during convalescence and following recovery (Cases 111 and 156, Figs. 8 and 9). In fatal cases very low levels have been found. The titer of opsonins has been found to parallel closely the patient's clinical condition. It has come to be regarded by us as a reliable index in determining dosage of antiserum, and as a valuable prognostic sign. In control cases treated with salicylates a similar rise of titer has been constant. An excessive dose of the vaccine of Streptococcus cardioarthritidis is followed by a prompt decrease of the opsonins and by the appearance of exacerbations of the focal symptoms of the disease, both with reference to the joints and to the heart. Patients with low opsonic indices are extremely susceptible to small doses of this vaccine. Graph II presents a composite curve of the opsonins in the sera of 10 patients with acute rheumatic fever. The observations cover a period of thirty days, during which time daily or semiweekly determinations were made. The low level upon first observation, the prompt rise and the maintenance of an elevated level are outstanding and regularly observed features.



GRAPH II.—Composite graph of the opsonic indices of 10 cases of acute rheumatic fever treated with antiserum.

These practical applications of the opsonic index have been one of the surprising developments of this work, since in the beginning the author shared the rather general skepticism concerning the value of this reaction. It has, however, proven to be the most helpful immunity reaction employed in this study. It may be apropos to recall that by means of this test, Tunnicliff[8] demonstrated the association of an immunologic group of streptococci with scarlet fever fifteen years in advance of the development of the serotherapy of this disease.

The prevalent ill repute of the test was responsible for the failure at the time to give her observations the attention which they deserved.

Action of the Antiserum of Streptococcus Cardioarthritidis in Rheumatic Fever and Chorea. Improvement follows the administration of the antiserum in rheumatic fever (Figs. 1, 2, 3 and 4, pp. 660, 661 and opp. 672). This becomes more and more significant as the number of patients treated increases. It has been observed in the acute arthritis, endocarditis, myocarditis, pericarditis, pleuritis, pneumonitis and subcutaneous nodules of rheumatic fever. This improvement is correlated with the quantity of antiserum administered. The severe cases require a larger total dosage than do the mild ones. It is not dependent on any immediate febrile nonspecific protein reaction following the injection of the serum, for it is observed in patients where no such febrile reaction appears. It is consummated before the period of serum disease. The full culmination of the effect of adequate dosage of the antiserum presents as its most striking feature the very apparent "detoxifying" of the patient, as presented upon clinical observation. The tense, anxious, pallid face takes on a relaxed, brightened appearance within twelve to twenty-four hours even before the tenderness and swelling of the joints has disappeared. Spontaneous pain in the joints is first eliminated. The tenderness and swelling are next in order to disappear. Frequently one is confronted with the condition of swelling of multiple joints in a patient who had received serum twelve to eighteen hours previously, with spontaneous pain and pain on motion entirely relieved and only very slight tenderness remaining on firm palpation. In other instances the patient will appear perfectly comfortable and nontoxic, even though physical examination yet reveals loud grating pericardial frictions, pleural rubs and patches of consolidation within the lungs. These are observations which do not appear in tabulations of joint symptoms nor in pulse, temperature and respiration charts. They are far easier to observe than to describe.

With the development of the concentrated antiserum, a more rapid introduction of the antibody was rendered possible through the marked decrease in the volume dose required. This appeared to have disadvantages, since the focal reactions referred to in Part II were observed with greater frequency. These reactions when referable to the joints cannot be differentiated clinically from the inflammation of joints primarily involved in the disease, except that there appears to be a peculiar predilection for such focal reactions to involve the small joints of the hands. Large joints primarily involved tend to clear up even in the presence of the milder grades of this reaction. The reaction may be differentiated upon experience by the general nontoxic appearance of the patient, even though temperature remains elevated, and by the immunity reactions with the patient's serum. The fractional dose method of administering

the concentrated antiserum is effective in preventing the more severe forms of such reactions, but not entirely efficient in preventing the milder forms. A more limited experience with private patients, not included in these studies, appears to demonstrate that the adminis-

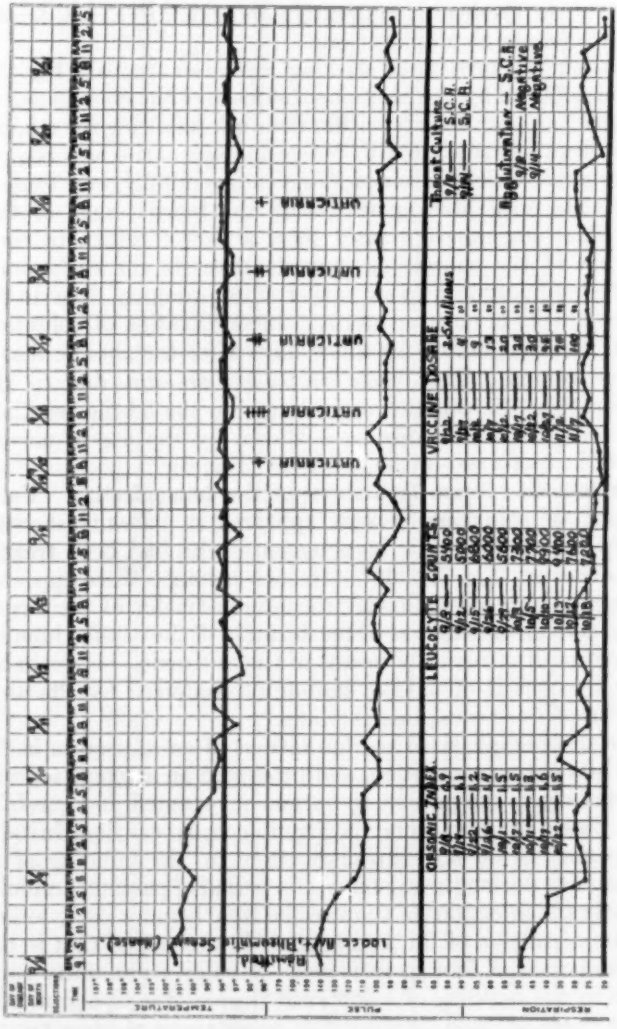


FIG. 11.—Chart presenting temperature, pulse and respiration curves of Case 169 (page 671). It indicates also the serum dosage, the period of serum disease, the opsonic indices, leukocyte counts, throat cultures, agglutination tests and the course of vaccine treatment.

tration of moderate doses of salicylates covering the few days on which the total dosage of serum is being administered provides a most effective method of preventing these focal reactions, as it does also in combating practically all of the manifestations of serum dis-

ease, except the urticaria. The observations on the effectiveness of salicylates in serum disease shed light on the action of salicylates employed alone in the treatment of rheumatic fever, and conversely suggest that the *exudative manifestations of rheumatism may be immunity reactions accompanied by fever.* An hypothesis of the dual nature of rheumatism (proliferative and exudative) will be the subject of a separate communication.

In Sydenham's chorea most striking responses appear (Fig. 5). These are manifested by the prompt subsidence of the choreic movement,[5] which disappear usually within the week following the administration of the antiserum, that is, before the serum sickness begins. The occurrence of violent serum sickness causes mild choreic twitchings to become noticeable again during the febrile stage of this reaction. The long-standing cases show a slower return to complete absence of the choreic movements than do the early ones. Speech defects appear to respond rather more promptly than do the choreic movements in most instances. Incoördination of voluntary movements usually persists for a few days after the choreic movements have ceased. That these responses are not due to the immediate nonspecific protein reaction, nor to the febrile reactions appearing with the serum disease is shown by the use of normal horse serum in treatment without benefit (Fig. 6).

Relapses following Serum Treatment: Active Immunization. Early in this work an occasional relapse appeared in patients showing grave, deep-seated rheumatic involvements, who had been treated with the antiserum (Fig. 7, p. 647). In each instance these appeared at from four to five weeks following the administration of the serum. This period corresponds to that of the duration of the passive immunity conferred in diphtheria by means of the antitoxin. It probably represents the period of passive immunity conferred by the antiserum of Streptococcus cardioarthritidis.

These relapses emphasized the limitations of an antiserum in the treatment of a chronic condition, and prompted an attempt to build active immunity in the patient by means of repeated and carefully regulated doses of a vaccine of Streptococcus cardioarthritidis. There appeared to be no contraindication to the building of an active immunity during the existence of a period of passive immunity consequently the injections of the vaccine were begun closely following the administration of the antiserum. It was hoped that in this manner the period of four to five weeks of passive immunity could be utilized in the building of a sufficient degree of active immunity to prevent these relapses. In a much larger series of cases treated since this practice was started, these relapses have occurred much less frequently. This has now become a routine practice. Naturally as yet observations extend over far too short a period to evaluate the ultimate effects of this procedure.

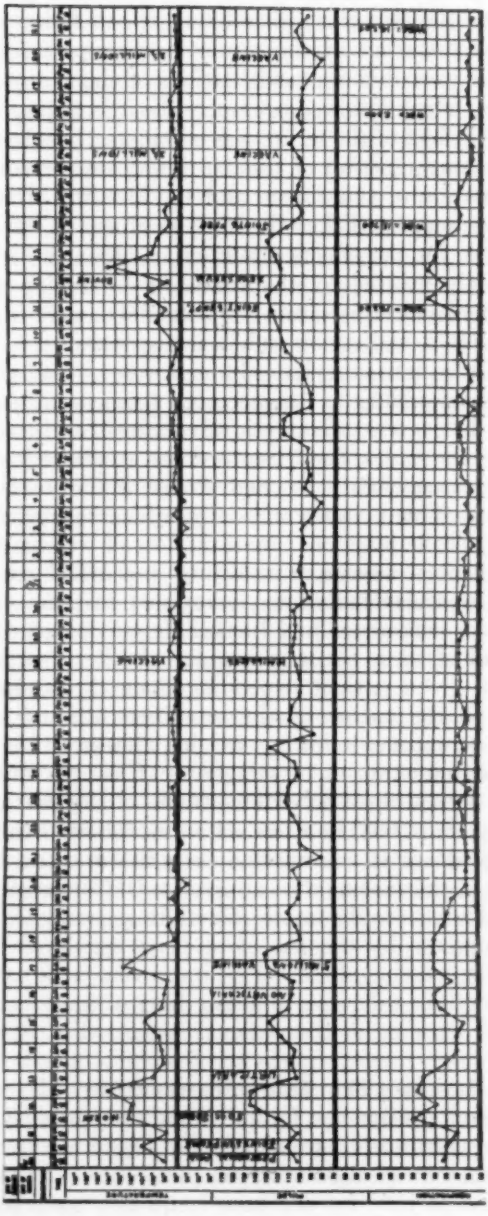


FIG. 7.—Case 133. Condensed pulse, temperature and respiration record of patient showing a relapse after serum treatment, with notations of serum dosage, pain, urticaria, vaccine dosage and leukocyte counts.

Experiences Suggesting the Presence of Toxic Products of the Bacterium in an Early Lot of the Antiserum. During a period in the development of the antiserum, deleterious effects followed the clinical trials of a single lot of the serum in rheumatic fever and in chorea. These were definite exacerbations of the symptoms of the existing disease which followed promptly the injection of the serum.

This harmful effect of the serum was eliminated in subsequent lots by allowing a longer period of time to intervene between the last massive inoculation of the animal and the bleeding of the animal. This experience suggested that the toxic products of the bacterium were responsible for the effects observed and that the antigen had not been entirely utilized by the animal in producing antibodies. The patients receiving this serum with ill effects were immediately placed on salicylate medication and their responses were those to be expected with adequate salicylate administration in rheumatic fever.

Individual Susceptibility to Streptococcus Cardioarthritidis Vaccine. Patients with deep-seated rheumatic affections in addition to showing a low opsonic index for Streptococcus cardioarthritidis, also show extreme susceptibility to small doses of the vaccine of this microörganism. This manifests itself by exacerbation of the joint symptoms, by febrile reactions, anorexia, loss of weight, abdominal distress, tympanites, nausea or vomiting, precordial pain, cardiac irregularities, muscular twitchings, emotional instability, wakefulness, increase in leukocytes and further depression of the opsonic index. Not all of these occur in one and the same patient, those appearing in a given patient depending upon the severity of the reaction and on the nature of the prominent existing rheumatic lesions. The symptoms following vaccine appear to be controlled by adequate administration of salicylates (Case No. 161, Fig. 13, p. 673). The activation of subsiding attacks of rheumatic fever has (Case 111, Fig. 8, p. 668) in a few instances, followed the injection of unduly large doses of this vaccine early in our work, before the latent dangers of the vaccine were appreciated. Conversely suitably chosen cases of subacute rheumatic affections are rendered free from persistent symptoms by the use of properly regulated courses of injections of the vaccine alone. This improvement is attended by the development of a tolerance to larger doses of the vaccine and by an increase of opsonins in the patient's serum (Fig. 9, Case 156, p. 670.

Attempts to Develop a Skin Test for Susceptibility. In our earliest attempts to develop a skin test for individual susceptibility, bacteria-free filtrates of cultures in various types of liquid media were used. These attempts were disappointing, in that portions of the filtrates dilutions heated to 100° for one hour frequently gave reactions as pronounced as did the unheated portions. Upon gaining experience with the vaccine of Streptococcus cardioarthritidis in the treatment of chronic arthritis, an outstanding and puzzling feature was

the great variation in individual susceptibility to it. With an idea of estimating this individual susceptibility to the vaccine, it early became our practice to inject intradermally the first dose used in a course of vaccine treatment. Amounts of 100 millions of the bacteria were used at first and positive skin reactions were commonly observed. Later the amount of heat-killed bacteria to be injected for this skin test was reduced to 5 millions. Extended experience with the intradermal test employed in this manner has brought out the observations that this test does not indicate truly the individual's susceptibility to the vaccine, since individuals may show no noteworthy local reaction and yet present marked general and focal reactions lasting from three to five days following the intradermal injections. The local reaction is elicited commonly and consists of an area of transient cutaneous erythema surrounding a red papule (Fig. 10). The papule has in some instances persisted for from ten days to two weeks in patients receiving 100 millions of the killed microörganisms by intradermal injection.

These observations tended to suggest that the local reaction following intradermal injection of culture filtrates or of the vaccine did not depend entirely upon the direct irritating effects of the products used.

We have recently instituted a more elaborate routine of skin tests in which in addition to the vaccine, or bacteria free filtrates alone, similar dosages of these, admixed with antiserum and with normal serum, are used. The necessary controls with the normal and immune serums are carried.

This has brought out certain reactions best observed in patients with chronic rheumatic arthritis, which are most interesting. For example, a patient will not react locally to the vaccine alone, nor to vaccine mixed with normal serum, but will react to the vaccine mixed with the antiserum. Also a patient will show no reaction to normal serum, but will show a positive reaction to the antiserum. Our experiences with these tests have been far too meager to analyze, but they offer, even in this early stage, suggestive evidence of reactions, similar in type to what is known as the Arthus phenomenon. They open a most intricate and fascinating prospect for study.

They also suggest that positive skin tests with such products of streptococci may arise in *immune individuals* from the local fixation of the antigen antibody complex,[9] and should direct attention to the study of such reactions under adequately controlled conditions in an effort to determine the underlying nature of the local inflammatory reaction. It would appear that uncontrolled intradermal tests, as recently reported by Kaiser,[10] do not permit of an analytical interpretation.

The matter treated in this paper is summarized at the end of the next paper, which also contains all references and additional illustrations.

RHEUMATIC FEVER.

II. The Present Development of the Biologic Products of Streptococcus Cardioarthritidis and their Application in the Treatment of Rheumatic Diseases.

By James Craig Small, M.D.,
PHILADELPHIA.

Preparation of the Antiserum of Streptococcus Cardioarthritidis. Equine and bovine antiserum of Streptococcus cardioarthritidis, which have been prepared and applied clinically, have been found to be equally effective in the treatment of patients.* These antisera have been monovalent and bivalent, being prepared from one or the other or from both of the two strains—R_1 and R_9.[1] These strains were chosen because they were obtained from blood cultures in typical cases of rheumatic fever and also because they react differently toward lactose—R_1 not fermenting lactose, R_9 fermenting it. Monovalent antisera of these two strains have proved equally efficacious in therapeutic trials.

As compared with the serum disease following the administration of equine antiserum, that from bovine antiserum is very mild. In our experience it is the exception for patients to show severe urticaria during the period of serum disease following the administration of the bovine antiserum, while febrile reactions and arthralgia are rarely observed. With equine antiserum quite the converse is true. This advantage of the bovine over the equine antiserum deserves emphasis in serum therapy generally, but it is especially important in rheumatic fever, since severe serum disease has commonly as one of its passing consequences, the exhibition of severe arthralgia. This confuses the clinical picture and may, unless anticipated, be mistaken for a relapse of the arthritis of rheumatic fever.

The preparation of an antiserum of Streptococcus cardioarthritidis has involved a considerable amount of experimental work in the development or application of methods best suited to the purpose of hyperimmunization of animals chosen for its production. Horses appear to utilize the antigens of Streptococcus cardioarthritidis in building antibodies less readily than do cattle. Lacking a method of determining the potency of the protective action of the antiserum in experiments on animals, it became necessary to make clinical trials of the different lots of antiserum which showed sufficient amounts of opsonins and agglutinins to warrant such trials. These clinical trials have brought out quite definitely differences in the potency of different lots of the antiserum, but unfortunately esti-

* Quantity production of the antiserum has been made possible through the acilities of the Mulford Laboratories, of Philadelphia.

PHILADELPHIA GENERAL HOSPITAL.—(Daily Progress Record.)

Name of Patient: A. H. Case No. 171. Ward: Rheumatic Fever

Date.	Day of disease.	General condition.	Spontaneous pain in joints.	Joint pain on motion.	Tenderness of joints.	Stiffness of joints.	Swelling of joints.	Extra-articular pain.	Choreiform movements.	Sweating.	Char. of pulse.	Max. temp. q. 3 hr.	Specific treatment.	Urticaria.	Lymphadenitis.	W.b.c.
1927																
Nov. 7	15	Fair	B.W.; B.S.; L.Hand	B.W.; B.S.; R.K.	B.W.; B.S.; R.K.; L.Hand B.S-C.	→Do.	B.W.; R.K.; 4F.—L.H.	0	0	++	Good	101.0	0	0	0	
8	16	Fair	B.W.; B.S.; L.Hand	B.W.; B.S.; R.K.	B.W.; B.S.; R.K.; L.Hand	→Do.	B.W.; R.K.; 4F.—L.H.	0	0	++	Good	101.4	20 cc. No. 14215	0	0	21,200
9	17	Fair	R.S.; L.Hand	R.S.; L.W.; R.K.	R.K.; L.Hand	→Do.	R.K.; L.Hand	0	0	+	Good	101.0	0	0	0	18,400
10	18	Fair	R.S.; B.K.;	B.K.; R.S.	B.K.; R.S.	B.K.; R.S.	B.K.	0	0	+	Good	99.4	20 cc. No. 14215	0	0	17,200
11	19	Good	0	L.K. (set.)	L.K. (set.)	L.K.	0	0	0	+	Good	99.4	0	0	0	10.500
12	20	Good	0	R.S. (set.)	0	R.S.	0	0	0	+	Good	99.4	0	0	0	8,800
13	21	Good	0	0	0	0	0	0	0	+	Good	98.6	0	0	0	
14	22	Good	0	0	0	0	0	0	0	±	Good	98.2	0	0	0	9,000
15	23	Good	0	0	0	0	0	0	0	±	Good	98.4	0	0	0	6,000
16	24	Good	0	0	0	0	0	0	0	±	Good	99.0	0	0	0	10,400
17	25	Good	0	0	0	0	0	0	0	±	Good	99.4	Vaccine 5 m. S.	0	0	9,000
18	26	Good	0	0	0	0	0	0	0	0	Good	98.8	0	0	0	9,200
19	27	Good	0	0	0	0	0	0	0	0	Good	98.8	0	0	0	7,200
20	28	Good	0	0	0	0	0	0	0	0	Good	98.8	0	0	0	
21	29	Good	0	0	0	0	0	0	0	0	Good	99.0	0	0	0	11,000
22	30	Good	0	0	0	0	0	0	0	0	Good	98.8	Vaccine 10 m. S.	0	0	8,400
23	31	Good	0	0	0	0	0	0	0	0	Good	98.8	0	0	0	14,400
24	32	Good	0	0	0	0	0	0	0	0	Good	99.0	0	0	0	9,000

Fig. 14.—Case 171. (See p. 674.) Progress record indicating the joints involved, maximum daily temperature, etc., "w.b.c." refers to leukocyte counts; *S* to sensitized vaccine; "5 m." and "10 m." refer to 5 and 10 millions of microörganisms in vaccine doses. Abbreviations: B.W., both wrists; B.S., both shoulders; R.K., right knee; B.S.C., both sternoclavicular joints; B.K., both knees; L.W., left wrist; R.S., right shoulder, etc.

mates of the therapeutic effects in patients cannot be utilized in an accurate standardization of the product.

The different lots of the unconcentrated antiserum have had to be used in amounts varying from 25 to 200 cc. in bringing about equivalent clinical responses.

Antiserum concentrated by the globulin precipitation method has been prepared. This when used in amounts of from 10 to 40 cc. has yielded uniformly very striking therapeutic effects in patients with acute rheumatic fever, or chorea (Case 171, Fig. 14, p. 651). The acute cardiac involvements as well as the peripheral manifestations of the disease respond promptly. The concentrated antiserum (equine) represents the most effective product prepared to date. Concentrated antiserum (bovine) is in process of preparation.

Application of the Antiserum. In view of the rapidity of the development of serious cardiac involvements in acute rheumatic fever, it is desirable to employ the antiserum as early as possible, but the presence of serious cardiac lesions does not contraindicate its use. When hypersensitiveness to horse serum is exhibited by a patient, treatment with the bovine antiserum is indicated, or *vice versa*. This is decidedly preferable to any attempt at desensitization. Accelerated serum disease usually arises where such attempts are made, and may, through its manifestation of arthralgia, add to the arthritis before sufficient absorption of the antibody content of the antiserum can control the rheumatic involvement. In such patients allergic reactions from the serum may on occasion mask the specific effects of the antiserum and add to rather than alleviate the patient's discomfort arising from the arthritic manifestations of rheumatic fever.

It is, therefore, highly important to make intradermal tests for hypersensitiveness before undertaking serum therapy. In these tests it is best to use plain or normal serum instead of the contemplated therapeutic antiserum, in order to avoid the possible chance of confusing a true allergic reaction with an entirely different local inflammatory reaction arising at times in individuals from intradermal injections of an antiserum. This latter reaction appears to be associated with the local fixation of antigen and antibody,[9] somewhat of the nature of the Arthus phenomenon. This reaction arises more tardily than the true serum allergic reaction, a fact which should easily enable its differentiation. It can be demonstrated in patients by making separate intradermal tests with the antiserum and with plain serum of the same animal species. Under favorable conditions a local inflammatory reaction arising from the antiserum, but not from the plain serum, is indicative of this phenomenon.

The existence of this reaction in certain patients suggests that well-marked focal reactions of a similar nature may arise following the administration of the antiserum. These may appear with reference to the heart lesions, as well as to those of the joints, and

consequently they represent a more serious condition, so far as the patient's welfare is concerned than do the milder grades of true serum allergy.

The arthritic manifestations of serum allergy, and these focal reactions following antibody administration are most difficult to differentiate from each other, and from the arthritis of rheumatic fever. These focal reactions seem to appear rather consistently following rapid, or excessive administration of the antiserum of Streptococcus cardioarthritidis. In severity they appear to vary directly with the amount of antibody injected independent of the volume of serum containing it. These observations suggest that such reactions are specific in nature, perhaps depending on the local fixation of the antigen-antibody complex.

Such specific inflammatory reactions appear to depend not entirely on the union of antigen and antibody, but to a considerable extent on the union in proper proportions of these two components.[9] Since antigen in acute rheumatic fever may be considered to be the factor responsible for the severity of the clinical manifestations of the disease, its concentration can be adjudged from clinical observation in the same manner as one estimates the amount of antiserum likely to be required in the treatment of a particular patient. A safeguard against this focal reaction lies in the proper regulation of the rate at which antiserum is administered and in the manner of its administration. The object is to prevent the sudden union of the entire amount of antigen in the toxic patient with its sufficient amount of antibody. This may be accomplished by following the paradoxical custom of giving the antiserum gradually in divided doses to those patients who appear the most acutely and gravely ill. This precaution is especially important when serious cardiac involvements are present. It is less important in chorea and in the various mild and subacute forms of rheumatic fever. It is less important also in patients who are on salicylate medication, since this appears to counteract such focal reactions.

The concentrated antiserum is preferable for therapeutic use, since its effective dosage is represented by a volume of about one-sixth that of the unconcentrated antiserum. The dosage of the concentrated antiserum ranges from 10 cc. to 40 cc.,* depending on the severity of the clinical condition. A safe rule is that of giving not more than 10 cc. of this product by intramuscular injection as the first dose. A second dose of like amount is administered after eight to twelve hours and, if more is necessary, a third injection

* This volume dosage is based on experience with the early lots of concentrated equine antiserum. Limited experience with subsequent lots of equine and the first lot of bovine concentrated antiserum indicates that a total volume dosage of from 5 to 15 cc. is adequate. It is not improbable that even higher potency may be attained and further reduction of volume dosage be made possible. Reduction of total dosage requirements will proportionately effect the amounts suggested in the fractional-dosage method.

after another twelve to eighteen hours of from 10 to 20 cc. may be used. The effects of the serum are observed upon its absorption in the alleviation of the outstanding symptoms. The complete absorption of an intramuscular injection is perhaps obtained within forty-eight hours after its administration.

If severe serum sickness arises it is usually initiated by general lymphadenopathy, followed in order by general malaise, urticaria, increase in temperature and in the pulse rate, and by pain and stiffness in the joints. The arthritic manifestations are usually most pronounced on the first and second days after the urticaria has subsided. Serum arthralgia is best differentiated from a relapse of the arthritis of rheumatic fever by a leukocyte count, which in this stage of serum disease shows a leukopenia. In no case should further injections of serum be practised at this stage.

Applications of Vaccine of Streptococcus Cardioarthritidis. The dosage of vaccine which may be employed in patients varies greatly with the individual, and the character of the clinical manifestations presented. As experience with the vaccine increased, the dosage was radically decreased, as its latent dangers came to be more and more appreciated. It should not be employed in the acute form of rheumatic fever, nor in patients showing a retarded convalescence from acute rheumatic fever. Serious extensions of the disease may result in the former, while sharp exacerbations may be precipitated in the latter. Such patients should first be treated with adequate dosages of the antiserum. The vaccine may then be used, provided its use is begun before the period of passive immunity conferred by the antiserum has passed. The administration of the vaccine may be started closely following the injection of the last dose of the antiserum, or one may wait until after the stage of the serum disease has passed before beginning this treatment. Vaccine is administered subcutaneously, and the interval between injections has been from five to seven days.

A starting dose of not more than 1 million of the microörganisms may be used. Subsequent dosage must be regulated according to the tolerance of the patient. In the course of the development of the vaccine treatment suspensions of at first 1000 millions, then 500 millions, 100 millions, 10 millions and finally 1 million per cc. have been used. Initial doses varying from 100 millions to 1 million have been injected in a volume of 0.01 cc. Later, with the more dilute vaccines, initial doses of from 1 to 0.1 million were injected in a volume of 0.1 cc. The severity of the primary actions following these doses did not appear to be so intimately related to the bacterial content as they did to the volume of the vaccine injected. This suggested that the substance responsible for these reactions is soluble in the menstruum in which the microörganisms were suspended. Further observations showed that suspensions of the microörganisms containing as little as 10 millions per cc. imparted

to the menstruum a concentration of this substance which approximated that imparted by 100 millions per cc. Dilution of the vaccine from 100 millions to 10 millions per cc. enhanced the reaction to dosages of corresponding numbers of microörganisms, since a larger volume was injected in the case of the weaker vaccine.

The general and focal reactions following vaccine administration usually become manifest at from twenty-four to forty-eight hours after its injection subcutaneously. Occasionally they appear on the third or fourth day and more rarely they may become evident as early as twelve hours after injection. The symptoms are quite diverse, as indicated above. The reaction gradually reaches a maximum intensity and subsides slowly. Moderate reactions last about three days. Severe ones are prolonged to seven days or more and are detrimental to the patient.

In patients receiving injections at intervals of two weeks moderate primary reactions of this type have been noted to pass, and a secondary reaction of similar type to appear, which attains its height on from the tenth to the fourteenth day. The analogy between these reactions and the delayed local reactions following intradermal injections of streptococci in rabbits as observed by Swift[11] is striking.

This secondary reaction constitutes a serious obstacle in vaccine therapy, since the delayed reaction of a particular dose may be superimposed on the primary reaction of its succeeding dose, and yield combined reactions of severe intensity. Experience has demonstrated that reactions far in excess of what might reasonably be expected, as judged from the responses to initial doses, arise frequently in the course of a series of vaccine injections. The secondary reactions appear to be related in severity to the number of microörganisms injected. These have been explained on the basis of the patient becoming sensitized to the vaccine after receiving several injections. Whatever may be the explanation of the secondary reaction, it is reasonable to regard it as being intimately concerned in these unduly severe reactions occurring in the course of vaccine treatments.

Streptococcus Cardioarthritidis Soluble Antigens. Because, within certain limits, the severity of the primary reactions following vaccine injections appears to be vary directly with the volume of the dosage rather than its bacterial content, and with the idea of eliminating the secondary reaction, the severity of which appears to depend on the bacterial content, the use of vaccine has been replaced by that of a bacteria-free filtrate prepared from suspensions of the microörganisms in normal saline solution. This, for convenience is designated "soluble antigen of Streptococcus cardioarthritidis." It contains the substance responsible for the primary reactions in a given concentration, which may be diluted as required. The dosage for obtaining a desired effect is then more easily regu-

lated. Secondary reactions have not been noted following its use, which, however, has not been as extensive as the application of the vaccine. This soluble antigen is prepared by suspending the microorganisms in normal saline in a concentration of 100 millions per cc. After a period of seven days in the refrigerator the bacteria are removed by filtration. The filtrate is then diluted with normal saline in making up the several dilutions for clinical use. Dilutions of 1 to 10,000 and of 1 to 1000 provide two stock solutions, which clinically have been found to be convenient in regulating dosage.

In patients who have received adequate amounts of the antiserum, active immunization may be started as early as the third day after the last injections of the serum. The 1 to 1000 dilution of the antigen may be employed in an initial dosage of not more than 0.1 cc. subcutaneously. Subsequent doses are administered at five-day intervals, and the amounts gradually increased through a course of eight to ten injections until 1-cc. dosage is reached. This latter amount should not be exceeded even though further injections are used. The successful use of the more concentrated antigen in such cases depends upon the free antibodies present by virtue of the administration of the antiserum in excess of the amount required for the immediate needs in counteracting the acute toxemia. When there is doubt of such excess of antibodies, as adjudged from clinical responses to the antiserum, the 1 to 10,000 dilution should be employed as indicated below.

In certain cases of subacute and chronic arthritis which appear to belong to the rheumatic group, the soluble antigen may be used in treatment without the previous use of antiserum. Great caution is necessary here, since patients differ markedly in their tolerance for the antigen. When doses which are too large for the patient are used there is a definite activation of the rheumatic condition accompanied by increased pain, stiffness and swelling in the joints, by anorexia, loss of weight, etc. Soluble antigen, 1 to 10,000 dilution, is administered subcutaneously at five-day intervals. The initial dose should not be larger than 0.1 cc. The subsequent doses are increased gradually, usually by 25 to 50 per cent increments, up to 1 cc. of this dilution. Thereafter the 1 to 1000 dilution may be continued with gradually increasing doses until 1 cc. of this dilution is tolerated.

If at any time during the treatments an injection excites a focal reaction which has not subsided at the end of five days, the next subsequent injection is withheld until the reaction has subsided and no increase in the size of the dose should be made. After it is shown by the repetition of such a dose that the patient has gained a tolerance for it, gradual increase in dosage may be again practised. Should such a reaction be excited by the initial dose of antigen, it is best to reduce the dose next administered to half of this amount, or, still further, if necessary, until a starting dose is found which can be tolerated by the patient.

Discussion. Failures in the treatment of suitable patients with these products are likely to arise from insufficient dosage of the antiserum and from overdoage of the soluble antigen. With the insufficient dosage of antiserum even the partial neutralizing effects obtained benefit the patient proportionately; but with the soluble antigen overdosage works distinctly harmful effects on the patient in further extending the existing disease processes. Conservative methods in the application of these agents, therefore, are concerned with liberal dosage of the antiserum and cautious dosage of the soluble antigen. Excessive dosage of the antiserum is to be avoided because of the focal reactions previously discussed. The soluble antigen is the most difficult of the two to apply properly in the treatment of the particular patient. Some criteria for estimating the patient's susceptibility to this product are necessary. We do not claim to have these fully elaborated, but our experience thus far dictates as follows:

(*a*) Do not use soluble antigen in the treatment of acute rheumatic fever or chorea, except as it may be employed following primary treatment with adequate amounts of the antiserum.

(*b*) A dose of soluble antigen which excites a febrile reaction is to be considered too large.

(*c*) A dose which excites severe focal symptoms in the joints, or referable to the heart, nervous system or gastrointestinal tract is to be considered too large if such symptoms persist on the fifth day after the injection.

(*d*) An accelerated pulse rate follows the injection of soluble antigen, and this symptom has come to be regarded as the most delicate indicator of the severity of a reaction. It may persist longer than five days after an injection, and subsequent injections should be regulated as to time of administration and amount injected by careful observation of the interval required for the pulse rate to decline to the preinjection level. The accelerated pulse rate appears to be related to a decline in blood pressure.

(*e*) A marked decline in the opsonic index for Streptococcus cardioarthritidis in the patient's serum following an injection of the soluble antigen is a reliable indication of overdosage.

(*f*) The patient who shows a loss in weight from week to week is receiving doses which are too large. Proper dosage promotes a gain in body weight.

Subacute and Chronic Rheumatism. While aware of the contention of some that rheumatic fever is never followed by chronic arthritis as a sequel, we have never seen evidence to prove this view beyond question. On the other hand, the specific therapy, which we believe we have in the biologic products of Streptococcus cardioarthritidis, may now enable us to select from the large group of chronic arthritides a smaller group which is related to rheumatic fever and Sydenham's chorea. The chronic character of rheumatic lesions in

the heart has been amply demonstrated by clinical and pathologic observations. Is it not reasonable to suspect that chronicity may be a character of tl lesions of rheumatism in other structures, particularly in the joints? Without going further into such a discussion here, we wish to report briefly our experience with such cases: The criteria for selecting the patients who may be treated with benefit by the soluble antigen alone are not fully established. At present we attach importance to the clinical signs of activity of the arthritis, as well as the age and general health of the individual. Very active cases should receive antiserum first. Old and infirm individuals may not be good risks during severe serum disease, should it arise, and serum is, therefore, avoided in them. Moderately active cases do not require serum since they respond very well to the soluble antigen alone.

The two laboratory tests which aid most in deciding what method shall be employed are the opsonic index and the titer of agglutinins for Streptococcus cardioarthritidis in the patient's serum. Our present conception of the opsonic index is that it represents the best indication that we have of the patient's resisting powers (see previous paper). The titer of agglutinins we believe to be an indication of the activity or lack of activity, of growth of the streptococcus in the focal location of its implantation. Since antigen appears necessary for the maintenance of an elevated titer of agglutinins, we believe that such antigen is supplied in sufficient amount to maintain an elevated titer of agglutinins only when there is activity of growth of the microörganism in the patient's tissues. Active clinical cases of arthritis, according to this view, would be expected to present low opsonic indices and high agglutination titers. Quiescent cases would have high opsonic indices and negative, or low agglutination titers. The different intermediate grades of activity might show a variety of relative relationships of these two factors. Clinical observations appear to support these views. Patients with low opsonic indices are very sensitive in the soluble antigen and are best started by treatment with the antiserum. Those with high opsonic indices may be treated from the start with soluble antigen.

Patients with high titers of agglutinins sometimes present opsonic indices which are normal, or above normal, but yet they are very sensitive to the soluble antigen. Clinically such patients frequently show acute upper respiratory symptoms following an injection. This suggests that the general reactions following an injection depend in part upon increased activity of the Streptococcus cardioarthritidis harbored by the patient. It is a common observation that activity of growth of the infecting microörganism is excited by the injections of products prepared from cultures of it.

While beyond the scope of this discussion to consider the matter of differential diagnosis within the chronic arthritis group, it is well

to mention positive evidence in support of the possible diagnosis of a chronic phase of rheumatic fever. A patient with chronic arthritis, whether atrophic or hypertrophic in type, who shows marked general and focal symptoms following a subcutaneous injection of a small amount of the soluble antigen of Streptococcus cardioarthritidis (0.1 to 0.5 cc. of the 1 to 1000 dilution) will be definitely benefited by the antiserum, followed by properly regulated courses of injections of the soluble antigen. Such a trial injection of the soluble antigen, therefore, we believe constitutes the best test for identifying the cases of chronic rheumatism in the chronic arthritis group. The test is without danger to the patient, and usually causes him no more discomfort than he has previously suffered on many occasions. He will resort to antirheumatic medication as has been his custom, and upon sufficient dosage this will overcome the pain. In our experience the local reaction from the intradermal test cannot be relied upon, and at best it does not furnish nearly as much information as can be obtained from the subcutaneous injection.

Selected Case Reports. CASE 52.—C. S., a white school girl, aged sixteen years, and normally developed, was admitted on February 25, 1927, with an acute tonsillitis. Four days after the onset of tonsillitis, the acute arthritis began in ankles, knees and wrists. She had profuse sweating since onset of arthritis. She was admitted to hospital on the third day of the arthritis. The patient had never had a similar condition. The joints involved on admission were both knees, both hips, both ankles, both wrists, both shoulders (slightly) and metacarpal phalangeal joints.

The pharynx was injected and the tonsils cryptic. Pulmonary areas were clear, the heart appeared of normal size and a soft systolic murmur appeared over the mitral area.

The patient received 50 cc. of antirheumatic serum (equine) intramuscularly on February 26; and a second injection of 50 cc. on February 28. The response to this treatment is indicated on the accompanying charts. (Figs. 1 and 2.)

On admission throat culture showed: Streptococcus cardioarthritidis. The patient's serum failed to agglutinate Streptococcus cardioarthritidis. The blood culture was sterile. The urine showed a slight trace of albumin. The leukocyte count was 15,700.

Diagnosis. Acute rheumatic fever. On discharge, March 31, 1927, electrocardiogram was normal. There was a soft systolic murmur over apex. Condition—good.

This case illustrated the response of joints and the decline in pulse rate of a heart slightly damaged. It also illustrates the usual sequence of the lymphadenitis, urticaria, fever, arthralgia and leukopenia accompanying serum disease.

CASE 11.—J. G., a white boy, aged eight years, was admitted to the Children's Hospital on June 21, 1927, and discharged August 17, 1927. Six months prior to admission the patient was seized with acute pain and swelling of the joints. This arthritis affected most of the large joints and shifted from place to place. This patient had never had a previous attack of rheumatism. Since the onset, six months ago, the boy has never been free from soreness and stiffness in the joints. Two weeks prior to admission

PHILADELPHIA GENERAL HOSPITAL.—(DAILY PROGRESS RECORD.)

NAME OF PATIENT: C. S. Patient, No. 52. WARD: Rheumatic Fever

Date.	Day of disease.	General condition.	Spontaneous pain in joints.	Joint pain on motion.	Tenderness of joints.	Stiffness of joints.	Swelling of joints.	Extra-articular pain.	Choreiform movements.	Sweating.	Char. of pulse.	Max. temp.	Specific treatment.	Urticaria.	Lymphadenitis.	Arthralgia and w.b.c.
1927																
Feb. 25	3	Fair	B.K.; B.Hips; B.S.; BE.; B.W.; B.Hands	→ Do.	→ Do.	→ Do.	B.K.; BE.; B.W.; B.Hands	0	0	++	Fair	102.4	0	0	0	15,700
26	4	Fair	Do.	Do.	Do.	Do.	Do.	0	0	++	Fair	103.6	50 cc. serum	0	0	
27	5	Good	B.Hands	B.Hands	B.W.; B.Hands	B.W.; B.Hands	B.Hands	0	0	+	Good	103.2	0	0	0	
28	6	Good	L.Hand	L.Hand	B.Hands	B.Hands	B.Hands	0	0	+	Good	102.8	50 cc. serum	0	0	
Mar. 1	7	Good	0	0	0	B.Hands	B.Hands (slight)	0	0	+	Good	100.4	...	0	0	
2	8	Good	0	0	0	0	0	0	0	0	Good	100.0	...	0	0	
3	9	Good	0	0	0	0	0	0	0	0	Good	98.6	...	0	0	
4	10	Good	0	0	0	0	0	0	0	0	Good	98.8	...	0	0	8,200
5	11	Good	0	0	0	0	0	0	0	0	Good	98.6	...	0	++	
6	12	Good	0	0	0	0	0	0	0	0	Good	98.6	...	++	++	
7	13	Good	0	0	0	0	0	0	0	0	Good	98.6	...	++	+	
8	14	Good	0	0	0	0	0	0	0	0	Good	99.0	...	+	+	
9	15	Good	0	0	0	0	0	0	0	0	Good	98.8	...	0	+	6,400
11	17	Good	0	0	0	0	0	0	0	0	Good	98.8	...	0	+	
13	19	Good	0	B.S.; L.Hand B.T.M.	→ Do.	→ Do.	0	0	0	0	Good	102.0	...	0	+	+++
14	20	Good	0	L.Hand B.T.M.	→ Do.	→ Do.	0	0	0	0	Good	100.4	...	0	0	++
15	21	Good	0	0	0	0	0	0	0	0	Good	99.0	...	0	0	5,400

FIG. 1.—Case 52. Progress record indicating the joints involved, maxim daily temperature, leukocyte count, etc. Abbreviations: B.K., both knees; B.H., both hips; B.S., both shoulders; B.W., both wrists; B.E., both elbows; B.T.M., both temporomaxillary joints.

numerous slightly tender subcutaneous nodules appeared about the small joints of the fingers and on the head. The joints at this time became more acutely involved and there was considerable pain over the precordium.

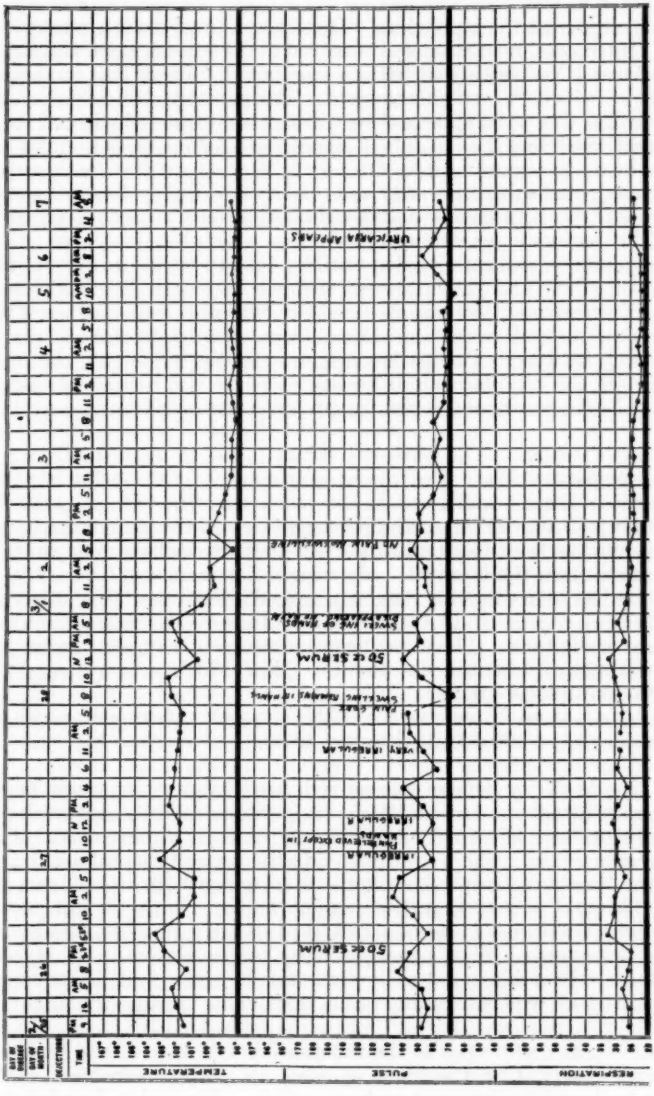


FIG. 2.—Case 52. Pulse, temperature and respiration records, with notations also of the dosage of serum, pulse and irregularities, urticaria, etc.

Upon admission the boy was very poorly nourished and very pallid. The knees were held in a semiflexed position, were not swollen but were extremely painful on attempts at motion. The fingers were held semiflexed and could not be extended without great pain. Attached to the tendons and joint capsules about the metacarpal-phalangeal and phalangeal joints were small, slightly tender subcutaneous nodules. The same appeared

along the tendons of the flexors of the wrist, over the back of the head; along the attachments of the ribs to the sternum and along the extensor tendon of the great toe. (See Figs. 3 and 4 in Part I.) The tonsils were enlarged, cryptic and evidently infected. The chest was very thin-walled and resonant throughout. The heart was enlarged to the left and the apex impulse was in the fifth interspace at the nipple line. There was a presystolic murmur over the apex. Intercostal retraction was observed in the second, third and fourth left interspaces. No pericardial friction was noted. There was tenderness over the liver, which showed enlargement. Temperature, 100.8; pulse, 130; respirations, 24. The child appeared very ill and was observed without specific treatment until July 2. On July 1 one of the subcutaneous nodules was excised for histologic examination. On July 2, 50 cc. of antirheumatic serum, equine, was injected subcutaneously and on July 5 a similar dose was given.

On July 7 the subcutaneous nodules showed a very evident decrease in size and the patient's general condition was somewhat improved. The pain in the joints on motion subsided until by July 16 he had entire freedom of motion of joints and subcutaneous nodules had entirely disappeared. The patient was given injections of vaccine of Streptococcus cardioarthritidis at five-day intervals, a few injections of iron cacodylate and was placed on a diet rich in liver. The patient gained rapidly in weight, the heart rate decreased, the valvular sounds became stronger and he was discharged on August 17 with a normal temperature, a pulse rate of 100 and respiration of 22.

Laboratory Findings. The patient's serum failed to agglutinate Streptococcus cardioarthritidis. The throat culture was positive for Streptococcus cardioarthritidis and the opsonic index was 0.9. On July 30 the opsonic index rose above normal and persisted so until the date of discharge.

This patient has been followed in the out-patient cardiac clinic since he was discharged from the hospital. His weight has increased from 37 to 54 pounds. He has been receiving regularly spaced injections of Streptococcus cardioarthritidis vaccine and has from time to time taken small amounts of the tincture of digitalis. There has been no return of any joint pains, nor any reappearance of subcutaneous nodules. The heart's action suggests an arrest of the pathologic process.

The blood count on November 14, 1927, showed: Hemoglobin, 80 per cent; erythrocytes, 4,300,000; leukocytes, 9800.

CASE 112.—M. T., a slender colored girl, aged twenty-two years, began to have a sore throat on April 5, 1927. A peritonsillar abscess developed and was evacuated. On April 12, choreic movements appeared and these rapidly became worse. She was admitted to St. Agnes Hospital and transferred to the Woman's Hospital on April 16. On April 19, a note from the Woman's Hospital stated that the patient had constant violent movements of limbs, trunk, head, face and talked constantly in an incoherent and unintelligible manner. She appeared very apprehensive and showed hallucinations. Bromides, morphine, chloral hydrate and hyoscyamus were administered without result. She slept none during the night of April 18.

The patient was transferred to the rheumatic fever ward of the Philadelphia General Hospital on the night of April 19. Upon admission every part of the body was in constant violent motion. She had to be placed in restraints because of violence of the body movements and talked and cried out constantly in a mumbling, incoherent fashion. The patient was hallucinated.

Diagnosis. Chorea insaniens.

The patient was given 50 cc. of antirheumatic (equine) serum on admission at 9.30 P.M. and luminal, gr. iss; chloral hydrate, gr. x; Na.Br., gr. xxx. She slept from 11 P.M. until 5 A.M.

April 20: The patient was quiet most of the day and sleeping a great part of the day. Choreic movements still very pronounced but less violent than night before.

April 21: The patient slept most of the day. The choreic movements were much less severe. The patient when undisturbed lies perfectly quiet for periods of from half to one hour. The restraints were removed; there is continued improvement.

April 22: The patient received a second injection of 50 cc. of the antiserum intramuscularly.

On the eighth day after the first injection of serum, or the fourth day after the second injection the choreic twitching had entirely disappeared. After two days of freedom from the twitchings, the febrile stage of her serum disease began. During this, very moderate twitchings were again observed. With the decline of temperature from the serum disease, the choreic movements disappeared. Slight manifestation of choreic movements during the febrile stage of serum disease has been rather constant in our series of cases of chorea.

The psychosis persisted for six to eight weeks, but cleared up entirely. There was no return of choreic movements. Bromides, luminal and chloral were used from time to time on account of patient's noisy condition, because of the psychosis.

This patient has remained in excellent condition. (Last observed February 16, 1928.) (Fig. 5.)

CASE 137.—H. C., a white girl, aged sixteen years, was admitted on June 13, 1927, transferred to the rheumatic fever ward on August 6 and discharged on September 26. She had been in the hospital on a number of occasions prior to this admission and for the past several years had been receiving institutional care almost continuously. She entered the hospital on May 22, 1926, from a convalescent home, with a very active attack of chorea, and was treated with sedatives and Fowler's solution. On July 23, she had improved sufficiently to be sent back to the convalescent house. Upon readmission on June 13, 1927, she presented a moderately active chorea which persisted practically unchanged upon transfer to the rheumatic fever ward on August 6, when she presented almost constant twitching of the fingers, and purposeless movements of hands and arms. There was little twitching of the muscles of the face. Pulse, temperature and respirations were normal. There appeared no gross cardiac involvement. She presented a blank expression of the face, refused to answer questions and was disinterested in her surroundings. She did not know how long she had been sick. As indicated on the tabulated record (Fig. 6) she was given two intramuscular injections of 50 cc. each of normal horse serum. The choreic movements became more pronounced on the third day after the first injection and remained so throughout and following the resulting serum disease.

Twenty days after the injection of the normal horse serum, the patient received antirheumatic serum (bovine) to the amount of 100 cc. in two intramuscular injections. The choreic movements disappeared entirely within eleven days. With the improvement, the patient's personality and facial expression underwent very remarkable changes. She would now talk and laugh freely with the other patients and her mental processes were much quickened. After being allowed to be up and about the ward, she took a great interest in waiting upon and assisting the other patients. She was discharged in excellent condition to the cardiac clinic for follow-up vaccine treatment. No sedatives were used.

Throat culture showed Streptococcus cardioarthritidis; the blood culture was sterile; the blood Wassermann test was negative. The patient's serum agglutinated Streptococcus cardioarthritidis up to dilutions of 1.20. The

PHILADELPHIA GENERAL HOSPITAL.—(DAILY PROGRESS RECORD.)

NAME OF PATIENT: M.T. Case No. 112. WARD: Rheumatic Fever.

Date.	Day of disease.	General condition.	Spontaneous pain in joints.	Joint pain on motion.	Tenderness of joints.	Stiffness of joints.	Swelling of joints.	Extra-articular pain.	Choreiform movements.	Sweating.	Char. of pulse.	Max. temp. ax.	Specific treatment.	Urticaria.	Lymphadenitis.	Arthralgia; w.b.c.
1927																
April 19	7	Fair	0	0	0	0	0	0	Restrained violent	0	Good	100.0	50 cc. 6482 E	0	...	14,000
20	8	Fair	0	0	0	0	0	0	Restrained violent	0	Good	101.8	...	0		
21	9	Fair	0	0	0	0	0	0	Moderate ++	0	Good	103.0		0		
22	10	Good	0	0	0	0	0	0	++	0	Good	102.4	50 cc. 6482 E	0		
23	11	Good	0	0	0	0	0	0	++	0	Good	103.4	...	0		
24	12	Good	0	0	0	0	0	0	+	0	Good	102.2	...	++		
25	13	Good	0	0	0	0	0	0	+	0	Good	102.0	...	++	...	7,300
26	14	Good	0	0	0	0	0	0	0	0	Good	101.2	...	0		
27	15	Good	0	0	0	0	0	0	0	0	Good	98.6	...	0		
28	16	Good	0	0	0	0	0	0	+	0	Good	102.0	....	0	..	6,800
29	17	Good	0	0	0	0	0	0	++	0	Good	102.4	...	+++		
30	18	Good	0	0	0	0	0	0	+	0	Good	100.4	...	0	...	8,000
May 1	19	Fair	0	0	0	0	0	0	++	0	Fair	104.6	...	0	...	6,500
2	20	Fair	0	0	0	0	0	0	++	0	Fair	101.0	...	0		
4	22	Good	0	0	0	0	0	0	+	0	Good	99.8	...	0		
6	24	Good	0	0	0	0	0	0	±	0	Good	99.2	...	0		
8	26	Good	0	0	0	0	0	0	0	0	Good	99.4	...	0		

FIG. 5.—Case 112. Showing the daily progress of patient with chorea. Severity of choreic movements indicated by (+) signs.

PHILADELPHIA GENERAL HOSPITAL.—(DAILY PROGRESS RECORD.)

WARD: R. F. 223

PHILADELPHIA GENERAL HOSPITAL.—(DAILY PROGRESS RECORD.)

NAME OF PATIENT: H. C. Case No. 137. WARD: R. F. 223

Date.	Day of disease.	General condition.	Spontaneous pain in joints.	Joint pain on motion.	Tenderness of joints.	Stiffness of joints.	Swelling of joints.	Extra-articular pain.	Choreiform movements.	Sweating.	Char. of pulse.	Max. temp.	Specific treatment.	Urticaria.	Lymphadenitis.	Arthralgia.
1927									+++							
Aug. 12	101	Good	0	0	0	0	0	0		0	Good	99.0	50 cc. N.H. serum	0	0	0
									+++							
13	102	Good	0	0	0	0	0	0	+++	0	Good	100.2	0	0	0	0
14	103	Good	0	B.S.	B.S.	B.S.	0	0		0	Good	99.0	0	+		
				B.K.	B.K.	B.K.			++++							
15	104	Good	0	B.S.	B.S.	B.S.	0	0		0	Good	99.0	50 cc.	+		
				B.K.	B.K.	B.K.			++++				N.H. serum			
16	105	Good	0	0	0	0	0	0	++++	0	Good	99.0	0	+++		
17	106	Good	0	0	0	0	0	0	++++	0	Good	100.0	0	+++		
18	107	Good	0	0	0	0	0	0	++++	0	Good	99.0	0	++	Vomited	
19	108	Good	0	0	0	0	0	0	++++	0	Good	102.0	0	0		
20	109	Good	0	0	0	0	0	0	++++	0	Good	100.0	0	++++	Vomited	
21	110	Good	0	0	0	R.S.	0	0		0	Good	99.4	0	0	...	+
						R.K.			++++							
22	111	Good	0	0	0	R.S.	0	0	++++	0	Good	98.6	0	0	...	+
23	112	Good	0	0	0	0	0	0		0	Good	98.6	0	0		
30	119	Good	0	0	0	0	0	0	++++	0	Good	98.6	0	0		
31	120	Good	0	0	0	0	0	0	++++	0	Good	99.6	50 cc. A.R. serum (bovine)	0		
Sept. 1	121	Good	0	0	0	0	0	0	++++	0	Good	99.0	0	0		
2	122	Good	0	0	0	0	0	0	+++	0	Good	98.8	0	0		
3	123	Good	0	0	0	0	0	0	++++	0	Good	99.8	50 cc. A.R. serum (bovine)	0		
4	124	Good	0	0	0	0	0	0	++++	0	Good	99.2	0	0		
5	125	0	0	0	0	0	0	0	++++	0	Good	98.8	0	0		
6	126	0	0	0	0	0	0	0	++++	0	Good	98.8	0	0		
7	127	0	0	0	0	0	0	0	++	0	Good	98.4	0	0		
8	128	0	0	0	0	0	0	0	+	0	Good	98.6	0	0		
10	130	0	0	0	0	0	0	0	+	0	Good	99.4	0	0		
11	131	0	0	0	0	0	0	0	+	0	Good	99.4	0	0		
12	132	0	0	0	0	0	0	0	0	0	Good	98.6	0	0		

FIG. 6.—Case 137. Showing the daily progress of a patient with chorea treated first with normal horse serum and subsequently with bovine antiserum. Severity of choreic movements indicated by (+) signs.

opsonic index for Streptococcus cardioarthritidis of patient's serum was below normal during observation following the normal horse serum, and promptly rose and remained above normal following the administration of antirheumatic bovine serum.

This patient serves as a control case, in that normal horse serum administration followed by a moderately severe serum sickness proved of no benefit, whereas antirheumatic (bovine) serum was followed by prompt improvement. It is noteworthy that practically no evidences of serum disease followed the use of the bovine serum. This is the rule rather than the exception following the use of bovine serum in our experience.

CASE 133.—E. B., a white girl, aged nine years, was admitted on June 9, 1927 and discharged September 3, 1927. Her chief complaints were shortness of breath and precordial pain. The child had rheumatic fever four years before and since that time has been treated for heart trouble. Two weeks, prior to admission she became ill, with fever, shortness of breath and pain over the heart. Upon admission she appeared as a fairly well-nourished white child, who had to be propped up in bed because of dyspnea. The extremities were cyanotic; the neck showed visible arterial pulsations; the chest expansion was somewhat limited, but fairly equal on both sides. There was an area of slightly impaired resonance at the angle of the left scapula, over which there was tubular breathing and pectoriloquy. There was definite precordial bulging. The cardiac apex impulse was indistinct. The left cardiac border extended beyond the anterior axillary line at the sixth interspace, while the right border measured 4 cm. from the midsternal line. At the fourth interspace a "to-and-fro" friction rub was heard. A mitral systolic murmur was also present and transmitted well out into the left axilla. The liver was palpable and tender. There was a moderate amount of stiffness in some of the large joints, but the arthritis was not a prominent symptom.

Laboratory Findings. The patient's throat culture showed Streptococcus cardioarthritidis, hemolytic streptococcus and Streptococcus viridans. Her blood serum failed to agglutinate antigens of Streptococcus cardioarthritidis.

Diagnosis. Pericarditis with effusion; rheumatic mitral disease and rheumatic myocarditis.

On June 11, the child received an intramuscular injection of 50 cc. of antirheumatic horse serum. This was followed by a prompt improvement in her general condition. On June 13 no pericardial friction rub could be detected and the liver had ceased to be tender on palpation. This child subsequently developed a moderately severe serum sickness, after which she continued temperature-free and symptom-free, except for a rapid pulse rate, until July 10, when there was a temperature elevation, accompanied by joint symptoms and precordial pain. Both the liver and spleen were palpable and tender at this time. The heart sounds were muffled, but no pericardial rub could be detected. (See Fig. 7; preceding paper, p. 647.)

The leukocyte count at this time was 17,200. A diagnosis of a relapse of rheumatic pericarditis was made and since the patient was sensitive to horse serum from the injection received one month prior, she was treated on this occasion with 25 cc. of antirheumatic bovine serum by intramuscular injection. Following this the patient's clinical condition began to show a prompt improvement, which continued until her discharge from the hospital. She has been followed since that time and has had no return of acute illness.

Fig. 7, represents the temperature, pulse and respiration rates over a period of about six weeks. This patient's record is presented to illustrate the period of passive immunity conferred by an injection of antirheumatic serum. It will be noted that this period is about one month. The case is of interest also in that it shows beneficial response to both anti-

rheumatic horse serum and antirheumatic bovine serum. It emphasizes a third consideration, in that the administration of the horse serum was followed by a moderate degree of serum disease, whereas the administration of bovine serum was followed by no serum disease. Vaccine was administered to this patient as indicated on the chart. It was administered in improper dosage on two instances only following the horse-serum treatment. Following the treatment with antirheumatic bovine serum, injections of vaccine were begun on the fourth day and continued at five-day intervals thereafter, until a dosage of 100 millions had been reached. The amounts of vaccine used in this course were as follows:

Two and one-half millions.	Twenty millions.
Two and one-half millions.	Thirty millions.
Four millions	Forty-five millions
Six millions	Seventy millions
Nine millions	One-hundred millions.
Thirteen millions.	

The last dose was administered on September 3.

CASE 111.—M. G., a colored woman, was admitted to the hospital on April 19, 1927. Her illness began early in March, 1927, with general malaise for several days followed by pain, tenderness and swelling in various joints. The knees were affected first, and later in succession the wrists, shoulders and elbows. She had been confined to bed for from a few days to a week at a time during the past two months, because of mild exacerbations of the arthritis. The patient denied previous attacks of rheumatism.

Upon admission her temperature was 99.8°; pulse, 96; respiration, 24. She appeared as a well-nourished, adult female, lying quietly in bed and appearing comfortable. She complained of slight stiffness in both knees and both shoulders, but was able to move her arms and legs without great discomfort. The heart was not dilated, the rhythm was regular and the valvular sounds were of good quality. There were no murmurs or thrills present. The blood count was: Leukocytes, 12,400; erythrocytes, 2,640,000; hemoglobin, 9.2 gm. per 100 cc.; polymorphonuclears, 60 per cent; lymphocytes, 39 per cent; mononuclears, 1 per cent. The urine showed a slight trace of albumin; the blood Wassermann test was negative. The throat culture was positive for Streptococcus cardioarthritidis and the patient's serum failed to agglutinate antigens of Streptococcus cardioarthritidis. The opsonic index was well above normal.

Diagnosis. Subsiding attack of rheumatic fever.

After several days rest in bed, without medication, the joints became entirely free. The patient was then given a large dose of vaccine of Streptococcus cardioarthritidis (500,000,000 subcutaneously). This was followed by a prompt drop in the opsonic index for Streptococcus cardioarthritidis. Six days later the opsonic index began rising and the patient was given a second dose of vaccine (250,000,000 subcutaneously). Following these two doses of vaccine, a very sharp exacerbation of rheumatic fever occurred. The temperature rose to 104.6 and multiple joints became acutely involved. The patient was placed upon moderate doses of sodium salicylate by mouth. Under this treatment the temperature promptly dropped to normal and the joints cleared up.

NOTE.—Fig. 8 presents the temperature curve, opsonic index curve, an estimate of the arthritis; dosage of vaccine used; the dosage of sodium salicylate in total number of grains per day. These curves show: (1) That an acute febrile attack accompanied by multiple acute arthritis followed the injection of two large doses of vaccine of Streptococcus cardioarthritidis; (2) this acute attack subsided promptly under moderate doses of sodium salicylate; (3) the opsonic curve showed a prompt suppression,

following the vaccine dosage, and during the acute febrile attack. It rose above normal following the use of sodium salicylate and remained above normal throughout convalescence.

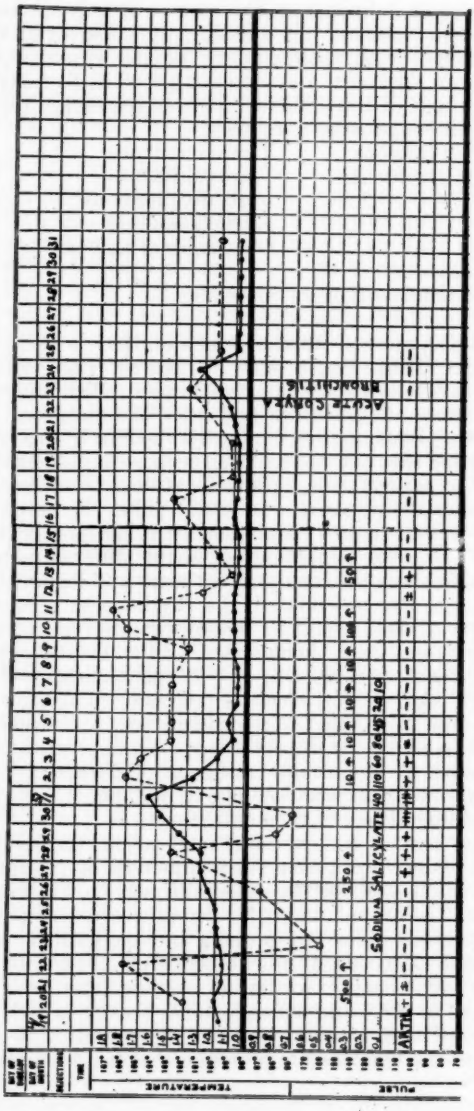


FIG. 8.—Case 111. Curves showing highest daily temperature (solid line) and opsonic index (broken line), as related to arthritis, vaccine dosage and salicylate administration. "500↗"; 250↗" indicate amounts of micro-organisms injected subcutaneously as the dose of vaccine. Figures for sodium salicylate indicate total dose for the day in grains. Acute arthritis is indicated by (+) signs.

Toward the end of her period in the hospital an acute coryza and bronchitis brought on an elevation of temperature without joint symptoms. It is interesting to note here that the opsonic curve for Streptococcus cardioarthritidis remained high during this attack in contradistinction to the febrile attack of acute arthritis, during which the opsonic curve was greatly suppressed.

CASE 156.—E. T., an adult white male, aged twenty-six years, was admitted on August 25, 1927, complaining of pain, tenderness and swelling of both knees and both ankles, and some pain on motion in both hips.

The attack began seven weeks before admission with acute involvement of the left wrist. Following this the left elbow, left shoulder, right knee and left knee became successively affected. He has had profuse sweating, considerable shortness of breath and precordial pain during the present illness.

The tonsils were removed at the age of six years. There is no history of chorea nor acute arthritis in childhood. The first attack similar to the present one, came on in December, 1925. It was accompanied by pain, swelling and redness of various large joints, by fever and profuse sweating. He was ill for seven weeks with this attack. During the interval since the first attack, the patient has had slight swelling and pain in various joints from time to time; but has never been forced to remain away from work because of this. Upon admission the patient appeared very pale, dyspneic, toxic and in intense pain. There was marked pulsation of the carotids. The tongue was heavily coated; the pulmonary areas were resonant throughout. The cardiac apex impulse was diffuse, in the fifth interspace and 13 cm. from midsternal line. The right cardiac border was 4 cm. from the midsternal line in the fourth interspace. Cardiac rhythm was regular at 118 beats per minute. The valvular sounds were of poor quality. A systolic murmur appeared over the mitral area and systolic-diastolic murmurs over the aortic area. Both knees and both ankles were swollen, tender and painful. Both hips were painful on motion.

Laboratory Findings. August 25, 1927: Urine, essentially negative; red blood cells, 3,680,000; white blood cells, 14,700; hemoglobin, 9.6 gm. per 100 cc.; polymorphonuclears, 76 per cent; lymphocytes, 24 per cent.

Throat cultures: Streptococcus cardioarthritidis; Streptococcus viridans; pneumococcus and Micrococcus catarrhalis.

Patient's serum agglutinates Streptococcus cardioarthritidis up to dilutions of 1 to 40.

Diagnosis. Acute rheumatic fever (recurrent). Rheumatic carditis with aortic and mitral insufficiencies and cardiac dilatation.

The patient received 100 cc. of equine antiserum by intramuscular injection on August 26, followed by improvement of the arthritis. There was a return of some pain in the involved joints and on August 30, a similar injection of an additional 100 cc. of antiserum was given. Following this joint involvements cleared up and the temperature declined. Severe serum disease began on the fourth day after the last injection.

Fig. 9 presents a temperature curve based on highest temperature for the day; the opsonic-index curve, antiserum dosage; vaccine dosage; an estimate of the arthritis and the leukocyte counts.

This case illustrates the decline of temperature, rise of opsonins and the decline of the acute arthritis as dependent upon an adequate dosage of the antiserum, the second dose of the antiserum being administered on the fourth day following an inadequate first dose. Severe serum disease followed the second injection rather closely. The fever, urticaria, arthralgia, early leukocytosis followed by leukopenia and the depression of the opsonic index accompanying the serum disease are clearly indicated.

Following the serum disease vaccine of Streptococcus cardioarthritidis was administered at five-day intervals. The first dose of 5 millions of the killed microörganisms was administered intradermally. A slight rise of temperature and a focal reaction in the joints followed. Locally this intradermal test was read as negative after twenty-four hours. Five days later a second injection subcutaneously of 2½ millions of killed microorganisms was followed by four days of elevated temperature and a focal

reaction in the joints lasting forty-eight hours. Repetition of this amount subcutaneously was tolerated five days later, as was also 5 millions after another five days.

The next dose was increased to 10 millions and a sharp reaction followed. To date the patient had received plain vaccine. He was now placed on a

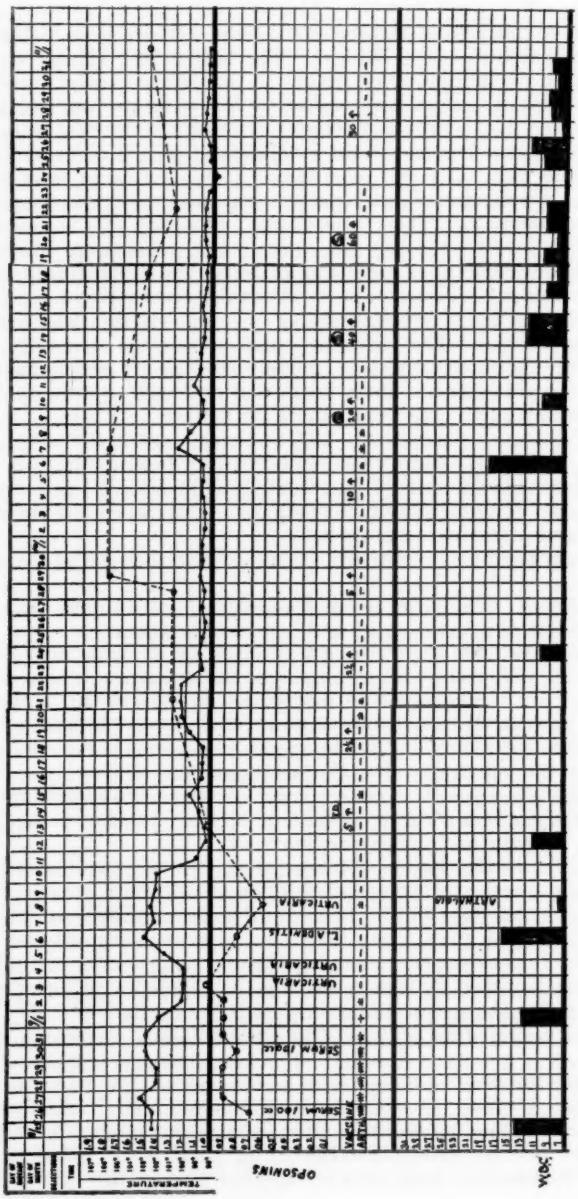


FIG. 9.—Case 156. Curves showing highest daily temperature (solid line) and opsonic index (broken line) as related to administration of antiserum and vaccine, to the acute arthritis and to the leukocyte counts. Acute arthritis is indicated by (+) signs and vaccine by numbers indicating millions of microörganisms constituting dosage. "*S*" refers to sensitized vaccine. "*I.D.*" refers to intradermal injection. All injections of vaccine except the first were injected subcutaneously "w.b.c., 7, 9, 11, etc." indicate leukocyte counts in thousands per c.mm.

sensitized vaccine in double the dosage of the plain and tolerated three injections, the last of which amounted to 60 millions of the bacteria. When returned to the plain vaccine subsequently a 30 million dosage was tolerated. Apparently during the treatment with sensitized vaccine, the patient had built up a tolerance to at least three times the amount of plain vaccine which had last caused sharp febrile and focal reactions. The increase in leukocytes following an injection of vaccine causing clinical reactions is unfortunately not illustrated in this chart. This, however, appears constantly. It is suggested in this chart by the high leukocyte count appearing on the day following the 10-million dose of plain vaccine, the last injection to cause a marked febrile reaction.

With the reactions following vaccines in addition there appeared increases in pulse rate, irregularities of cardiac rhythm and pain over the precordium. This patient has a seriously crippled heart. He has been placed in an occupation involving exertion commensurate with his cardiac reserve and his health continues excellent.

CASE 169.—B. B., a colored female child, aged ten years, was admitted on September 8, 1927, complaining of shortness of breath and pain over the precordium. Two years ago she had an attack of rheumatic fever with acute joint involvements and since has had several attacks of mild arthritis. Following the first attack two years ago the tonsils were removed. During the past two years the patient has on occasions shown considerable dyspnea and edema of the ankles.

The child appeared very ill on admission and had to be propped nearly upright in bed, because of the dyspnea. She complained of pain over the heart and showed marked tenderness over the liver. The area of cardiac dullness was greatly enlarged and was especially wide at the base of the heart. Traube's space was obliterated, the cardiohepatic angle rounded and the right lobe of the liver displaced downward and was tender. An area of impaired resonance, over which appeared bronchovesicular breath sounds, was noted posteriorly about the angle of the left scapula. A mitral systolic murmur was indistinctly heard.

Diagnosis. Rheumatic pericarditis with effusion.

September 8: The child received on admission 100 cc. of antirheumatic serum (equine unconcentrated) by intramuscular injection.

September 9: General condition is much improved. There is no tenderness over the liver today, nor any precordial pain. Dyspnea has disappeared. Patient can lie flat in bed. Little change in physical findings in regard to area of cardiac dullness. The response of this patient is indicated on the summary chart, Fig. 11. The response, so far as the heart is concerned, is presented graphically in the series of teleroentgenograms, Fig. 12. (See Figs. 11 and 12; preceding paper, p. 645 and opp. 672.)

The patient continued to do well and was discharged on November 9. The heart showed a rate of from 100 to 110 per minute, considerable hypertrophy, a systolic mitral murmur and accentuated second pulmonic valvular sound.

CASE 161.—H. J., a white woman, aged thirty-two years, was admitted on September 15, 1927, complaining of pain and stiffness in both knees and in the left ankle. The present attack began eight weeks before admission with pain in both feet, which she thought was due to fallen arches. Arch supports gave no relief. Several weeks later pain, stiffness and some swelling developed in both ankles and in the right wrist. There has also been involvement of the mandibular articulations, as well as stiffness of the neck.

The patient states that she had never had acute rheumatic fever nor chorea, but had "growing pains" after the age of ten years, which were

severe enough to cause her to remain in bed for several days at a time. Later she has had "muscular rheumatism" in the arms, legs and neck at various times. She has been treated for "heart trouble" since sixteen years of age. During the present attack, before admission to the hospital, she has been treated with salicylates. Upon admission, the patient, a large, pallid, white woman, appeared comfortable when lying quietly in bed. The temperature was 99.8° F.; pulse, 96; respiration, 24 per minute. The tongue was heavily coated. The tonsils were very large and appeared diseased. There were no abnormal signs over the pulmonary areas. The cardiac apex was in the fifth interspace; a blowing systolic murmur was heard over the apex and transmitted into the left axilla. There was stiffness, pain on motion and some tenderness of both knees, and the left ankle.

Diagnosis. Subacute rheumatic fever with mitral regurgitation.

This patient did not receive the antiserum, being used as a control case in studying the opsonic index curve and the effects following injections of the vaccine of Streptococcus cardioarthritidis. She had been receiving salicylates before admission. When placed in bed, without medication, for four days, there was a prompt recrudescence of the acute arthritis, and a temperature elevation to 102°, accompanied by a leukocyte count of 30,000 per c.mm. (See Fig. 13.) The opsonic index for Streptotoccus cardioarthritidis was below normal at this time. The patient was placed on moderate amounts of sodium salicylate. A prompt decline in the temperature and leukocyte count, accompanied by a clearing up of the involved joints followed. The opsonic index rose promptly with this improvement. While under 90 gr. of sodium salicylate daily, a large dose of the vaccine of Streptococcus cardioarthritidis was injected subcutaneously. This was followed by a prompt decline in the opsonic index, but by no elevation of temperature nor activation of the arthritis until after the dosage of salicylate had been reduced to from 20 to 30 gr. per day. Increased dosage of salicylate again appeared to control the fever and the arthritis, and under it the opsonic index, which had remained low for ten days, promptly rose above normal. Salicylates were now discontinued and moderate amounts of vaccine injected at five-day intervals. It will be noted that these small doses now were followed by temperature rises, increased joint manifestations and elevated leukocyte counts. The clinical course of this patient was unsatisfactory. She was discharged from the hospital still presenting an elevated pulse rate, a high leukocyte count, vague joint and muscle pains, an elevated agglutination titer and a normal opsonic index.

After further trial of small doses of the vaccine, this patient was readmitted on December 2, and treated with the antiserum, with an excellent response. She is being treated with injections of the soluble antigen of Streptococcus cardioarthritidis and continues to do very well. In this study as presented in Fig. 13 we note:

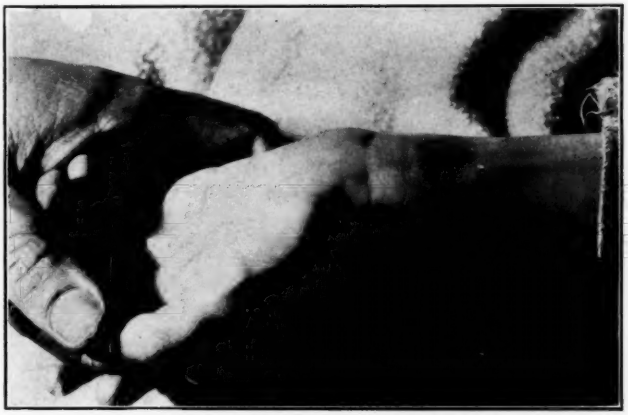
(*a*) A rise of opsonins under salicylate medication in rheumatic fever, with coincident decline in temperature, joint symptoms and leukocyte count.

(*b*) The febrile and focal reactions following a large dose of the vaccine of Streptococcus cardioarthritidis did not appear while the patient was under moderate amounts of sodium salicylate.

(*c*) The depression in amount of opsonins in the patient's serum occurred promptly following the large dose of vaccine while the patient was under salicylate medication.

(*d*) Fever and acute joint symptoms came on at the end of five days after the vaccine and when the amount of salicylate medication had been reduced. Increased dosage of salicylate again controlled these symptoms and under it the opsonic index again rose above normal.

a



b

FIG. 3, *a* and *b*.—Case 11. Subcutaneous nodules in rheumatic fever.

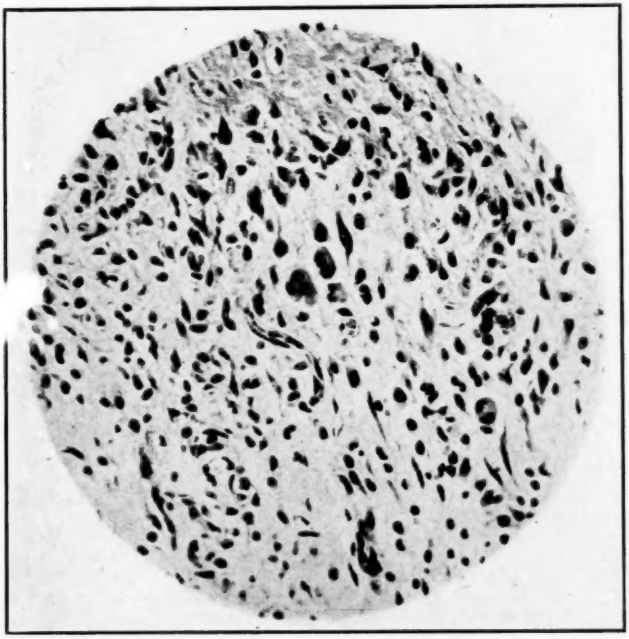
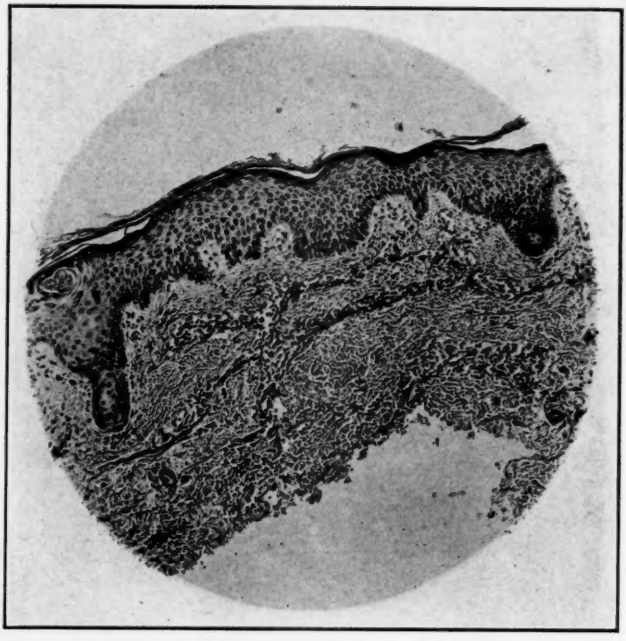
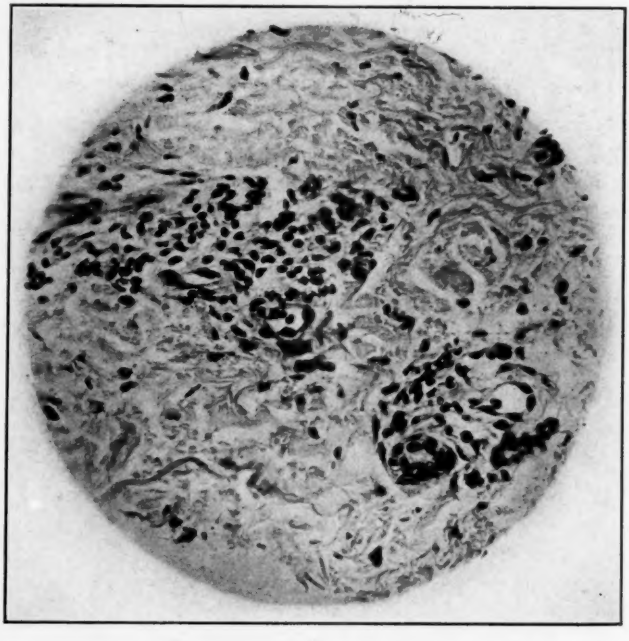


FIG. 4.—Histology of subcutaneous nodules from Case 11. Mag. × 320. Endothelioid cells, multinuclear giant cells, fibroblasts and bloodvessel changes.



a



b

FIG. 10.—Histology of a papule developing at the site of an intradermal injection of vaccine of Streptococcus cardioarthritidis (100 millions of microörganisms). Left forearm of a nonrheumatic individual excised ten days after the injection. Perivascular infiltration of small round cells and endothelioid cells. × 80 and × 320.

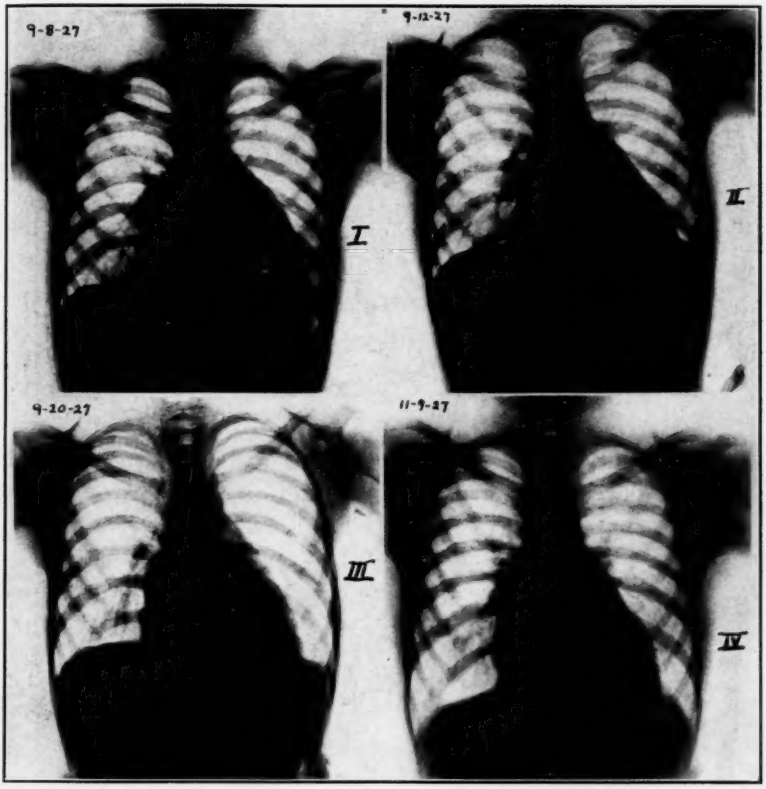


FIG. 12.—Teleroentgenograms in Case 169. No. I, on September 8, 1927, before treatment with antiserum; No. II, on September 12, 1927; No. III, on September 20, 1927; No. IV, on November 9, 1927.

(*e*) Much smaller amounts of vaccine administered when patient was receiving no salicylates were followed by febrile, focal and leukocyte reactions.

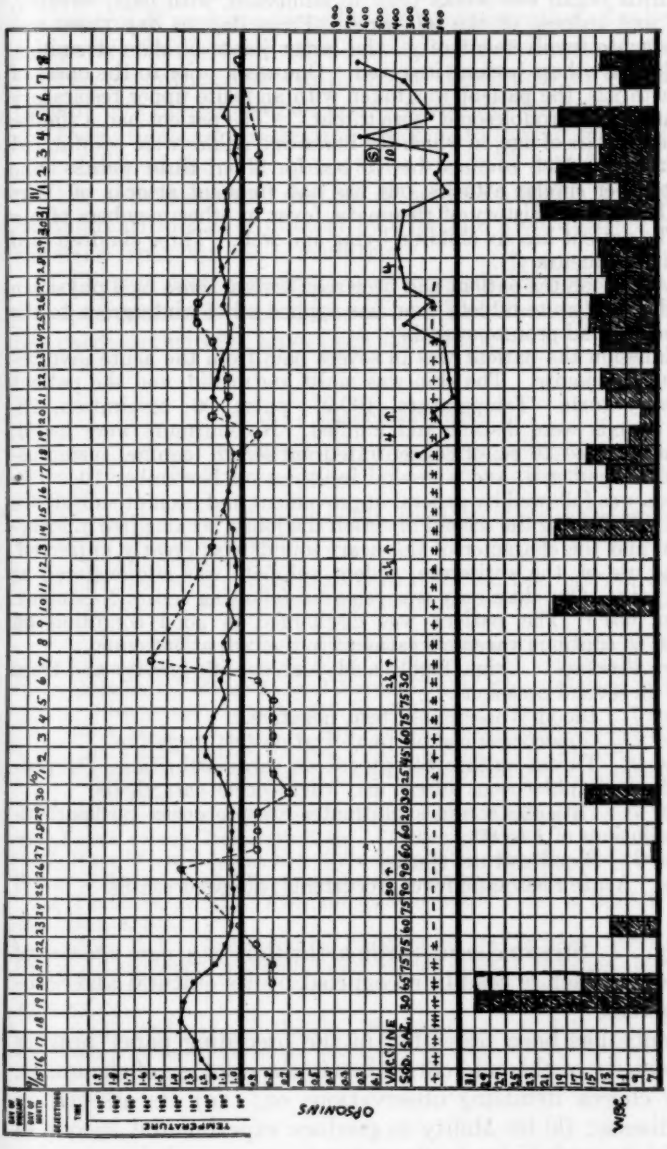


FIG. 13.—Case 161. Curves showing the highest daily temperature (solid line) and opsonic index (broken line) on upper dark base line; curve showing titer of agglutinins on middle dark base line; the vaccine dosage is indicated by numbers indicating millions of microörganisms injected; the dosage of sodium salicylate is indicated by numbers indicating total grains per day. The arthritis is indicated by (+) signs; "w.b.c., 7, 9, 11, etc." indicates leukocyte counts in thousands per c.mm. identified by the cross hatching on lower base line. *S* indicates sensitized vaccine.

This patient evidently could not tolerate the amount of vaccine employed in her treatment. She responded promptly to the antiserum and thereafter under treatment with products of the bacterium continues to do well.

CASE 171.—A. H., an adult white woman, aged forty-two years, was admitted on November 6, 1927, complaining of pain and tenderness of both wrists, both shoulders, right hip, right knee, the first, third and fourth fingers of left hand and both sternoclavicular joints.

The arthritis began two weeks prior to admission, with pain, swelling, tenderness and redness of the left wrist. From day to day there was progressive acute involvement of all the larger joints of the extremities, some receding as others became involved. One week prior to the onset of the acute arthritis, the patient was taken with an acute upper respiratory infection, and had a troublesome "sore throat." The patient had a similar attack at eight years of age, in which the knees and ankles were painful, red and swollen, and which confined her to bed for about three weeks. She has had no other similar attacks, but has had frequent attacks of "sore throat." There is no history of rheumatic fever in other members of her family. The patient has six children living and well. Three children died when small of influenza (?).

Prior to admission the patient had been seen several times by a physician and treated with "white tablets" and has applied oil of wintergreen to the joints. She has had profuse sweating.

Upon admission the patient was in severe pain from the acute involvement of multiple joints. The skin was moist and pallid, and the patient appeared very toxic. Temperature, 100.2°; pulse, 90; respiration, 28. The heart sounds were distant and muffled. No murmurs were heard. The patient received 20 cc. of concentrated antiserum (equine) intramuscularly, on November 8, and a second injection on November 10. The first injection was followed by general improvement and prompt subsidence of the pain. Following the second injection the joints became free in forty-eight hours, and the character of the heart sounds was greatly improved. Prior to the use of the antiserum, codein sulphate was administered as needed for pain. One dose only was required following serum treatment. (Fig. 14, p. 651.) The patient was discharged in good condition on December 1, to continue vaccine treatment in the outpatient clinic.

Laboratory Findings. Urine, highly acid; high specific gravity and trace of albumin on several occasions.

November 7: Blood Wassermann test, negative.

November 7: Gonococcus complement-fixation test, negative.

November 9: Throat culture Streptococcus cardioarthritidis, Streptococcus viridans; Staphlococcus aureus and Micrococcus catarrhalis.

November 7: Patient's serum agglutinates Streptococcus cardioarthritidis up to dilutions of 1 to 80.

November 7: Blood culture, sterile.

Diagnosis. Acute rheumatic fever (recurrent); diseased tonsils.

Summary. 1. Streptococcus cardioarthritidis is a new species of streptococcus, which is readily recognized by its cultural and serologic characters.

2. Evidence has been presented in the preceding paper bearing on the specificity of this microörganism in the etiology of rheumatic fever, and chorea itemizing observations on: (*a*) Its association with the disease; (*b*) its ability to produce experimental lesions in animals; (*c*) its agglutinins in the patient's serum; (*d*) its opsonins in the patient's serum.

In this paper are considered: (*a*) The favorable changes following the use of its antiserum in patients suffering with rheumatic fever,

chorea, rheumatic carditis, subcutaneous nodules, etc.; (*b*) the duration of the effects of antiserum alone; (*c*) the patient's susceptibility to the vaccine, or soluble products of the microörganism, as manifested by exacerbations of the rheumatic symptoms and lesions; (*d*) the control of such reactions by the administration of salicylates; (*e*) the parallelism between the development of increased tolerance to the vaccine or the soluble antigen and the clinical improvement of the patient; (*f*) the building of active immunity by means of vaccine or soluble antigen administration alone or following serum; (*g*) the improbability of the development of a local skin test for susceptibility; (*h*) the subcutaneous injection of soluble antigen of Streptococcus cardioarthritidis as a clinical test for the identification of patients suffering from chronic rheumatism.

3. Certain considerations, as at present developed, for governing the applications of the antiserum and soluble antigen of Streptococcus cardioarthritidis, have been discussed.

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CERTAIN FACTORS MILITATING AGAINST ACCURATE CORRELATION OF PHYSICAL AND ROENTGEN RAY EXAMINATIONS OF THE CHEST.*

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In the practice of clinical medicine today, when laboratory and mechanical methods are employed so generally in the investigation of the sick, it is necessary to evaluate and determine the limitations of each established method of examination if we would approach anything like accuracy. In this paper, I shall discuss some of the sources of discrepancy between physical and Roentgen ray examination of the chest in an effort to show why the results of these two methods are not always comparable.

The most accurate diagnosis and prognosis in a given case of illness can be made only by studying the manner in which the patient is able to carry on his body functions in spite of the disease; or, in other words, by carefully studying the symptoms present and combining this study with a competent physical examination of the patient himself. The results of laboratory and mechanical investigation are rarely to be interpreted as making the diagnosis but rather as strengthening or weakening the opinion gained by the careful examination of the patient.

I realize that this statement may be opposed by many who have learned to accept data obtained by the test tube and by mechanical devices as being more accurate than those obtained by clinical examination; nevertheless, it will appeal to that group of clinical observers who, while utilizing all methods, have especially trained the eye to see, the ear to hear, the fingers to reveal what they touch, and above all the mind to analyze and evaluate what is seen, heard and felt.

For years, physicians who have been devoting their attention to the study of the clinical phases of tuberculosis have noted that in many instances the results of physical and Roentgen ray examination of the same chest fail to reveal the same extent or the same intensity of the disease process. Sometimes the physical examination seems to reveal lesions that the Roentgen ray does not and often the Roentgen ray reveals something missed on physical examination. The tendency has been for the clinician to accept the Roentgen ray plate as being a true picture faithfully representing the lesions within the lung, and because of these differences to lose confidence in his ability to detect the amount of pathologic change in the lung by physical examination. This opinion of the relative value of the Roentgen ray and physical examinations of the chest has been so

* Abstract of Discussion before Los Angeles Clinical and Pathologic Society, September 22, 1927.

definitely established in the minds of a large group of clinicians that they send their patients to the Roentgen ray room before they make a physical examination; and endeavor to make their physical findings conform to shadows found on the plate. Not only is such a method to be greatly deplored because of its influence in underrating the value of physical examination, but even more so because it sets up in many instances an erroneous standard with which to compare physical examinations.

We have made it a fixed rule never to look at a plate until we have completed our physical examination, and in most instances until we have stated our opinion. In comparing the data from the two methods of examination, the evidence of the presence or absence of a probable tuberculosis will coincide in the great majority of instances, but the extent of signs on physical examination and the extent of shadows on the plate will quite often be at variance, and occasionally pathology will be suspected by one method, which is not revealed by the other.

In seeking an explanation for this variance, we were confronted by: (1) Certain well recognized sources of error in physical examination, and, (2) by certain errors inherent in the Roentgen ray. The results of physical examination, as well as the results of Roentgen ray examination, will differ according to the ability and experience of the examiner and operator. On physical examination, there are no signs or sounds that can be interpreted as always indicating a definite pathologic lesion, so the interpretation will depend on the examiner. The condition of the chest, aside from the pathologic changes due to the tuberculosis, must be taken into consideration. Especially must the remains of previous diseases, the compensatory changes that have taken place, and the condition of the pleura be considered. In this connection, the differentiation of pulmonary and extrapulmonary râles is attended with particular difficulty. Likewise, the character of the plate, the judgment used in proper penetration, the placing of the patient, the time of exposure and the experience in reading shadows are all generally recognized as influencing the plate reading.

But aside from this there are two very definite sources of error, which are not so well known, that I wish to discuss in this paper. One is due to the fact that, while different tissues intercept rays differently, yet pathologic tissue does not always intercept the rays more or to a sufficiently great degree to make pathologic processes stand out in shadow when compared with nonpathologic tissue. This was shown by Assmann[1] who made a careful comparative study of Roentgen ray and postmortem findings. He took plates before and after death and then sectioned the lung carefully, investigating every portion of the pulmonary tissue and comparing it with the plates. As the result of this critical study, he says: "At times the Roentgen ray shows details of unexpected minuteness; for example,

nodules scarcely as large as pin heads are at times shown, exact in position, size and relationship. Again, nodules as large as walnuts fail to appear on the plate and areas of thickened tissue even larger than this, cast no shadows or shadows which are scarcely recognizable. Aside from the thickness and specific chemical composition of the focus, the detail of the shadow which it produces depends upon its depth in the tissues."

In the examination of tuberculous patients, we have long been convinced that it is impossible to correlate physical and Roentgen ray findings too closely. When we were using exclusively in our Roentgen ray examinations stereoscopic plates taken dorsoventrally with a distance of 40 inches between the tube and the screen, we particularly noticed that the greatest discrepancy was found in comparing physical findings over the posterior wall of the chest with the plates. We then began taking plates ventrodorsally as well as dorsoventrally and found that the shadows on the plates of chests showing more disease posteriorly on physical examination also showed a greater density or more widely spread density when taken ventrodorsally than plates taken dorsoventrally and *vice versa*.

We should have suspected this from the fact that the scapulæ are well visualized in plates taken ventrodorsally, while they cast little or no shadow in plates taken dorsoventrally. This is of particular import because the scapula is made up of calcium, which intercepts the rays to a much greater extent than the softer tissues which make up the pathology of tuberculosis.

We then began to study our cases roentgenologically with plates taken both ways and found that when the greatest amount of disease was on the side of the lung nearest the plate it showed best; and that oftentimes when on the side away from the plate, the extent of the lesion was greatly minimized and at times even failed to be recorded. In comparing plates taken dorsoventrally with those taken ventrodorsally on the same day, with the same distance from tube, there was some difference in nearly all; in many, not sufficient to make any great difference in our opinion of the disease. In quite a few, however, there was a marked difference, and in some it was so great that when the two plates were placed side by side they would not be recognized as being those of the same chest. While stereoscopic plates, as compared with single plates, will eliminate some of this error they cannot eliminate it all, as will appear from our discussion of the factor in technique which is responsible for it. Our plates are all taken with the distance of 40 inches between the patient and the tube, the patient leaning firmly against the screen. We use the same distance and same method whether taken ventrodorsally or dorsoventrally.

I find that the basis for the above observation was established experimentally by Ziegler and Krause,[2] in 1910. They studied the effect on plates made by placing strips of lung containing tuber-

culosis lesions on the chest wall before Roentgen raying the chest. They found that when the strips were lying on the chest wall nearest the plate, they caused sufficient absorption of the rays to cast a shadow, but when on the side nearest the tube they influenced the plate little or not at all. As a result of these experiments they suggested that both dorsoventral and ventrodorsal plates should be taken in all cases where small lesions were suspected. Gräff and Küpferle have also discussed this phase of the subject in two valuable communications.[3, 4]

Probably the best suggestion that has been made for overcoming this difficulty is that of Groedel,[5] who considers that the chief difficulty in securing proper definition of lesions situated in that portion of the lung nearest the tube is due to the secondary rays which come from these lesions, the effect of which can be overcome by taking films with the tube two meters from the patients, and instead of the patient standing directly against the screen, by placing the screen at a distance of 20 cm. from the surface of the body.

Since so much dependence is being placed on the Roentgen ray in diagnosis, and since errors in diagnosis of early tuberculosis may prove to be so costly to the patient, it is necessary that the nature and cause of inaccuracies be understood so that methods for overcoming them may be devised; and, if this proves to be impracticable, so that the fact of the existence of error at least be generally known.

Roentgen Ray Shadows Depend on the Chemical Composition of Tissues. In order to determine the true place of the Roentgen ray in the examination for chest diseases, it is necessary to understand what the Roentgen ray plate is and what it is capable of showing. A Roentgen ray plate of the chest is a composite picture in which many different structures take part. The variations in the plate are due to the way in which different structures interfere with the passage of the Roentgen rays and the manner in which the shadows from such structures are superimposed upon each other. The obstruction of the rays follows definite laws, the understanding of which is necessary to the appreciation and the interpretation of the plate. The rays are obstructed to a different degree by different tissues and different pathologic processes, because different elements enter into the composition of the various tissues and pathologic processes.

The power of the physical elements to obstruct rays varies approximately with the fourth power of their atomic number.[6] The elements which make up the structure visualized by the chest plate are those found in the normal and pathologic intrathoracic tissues, the air in the lungs, and the bones and soft structures composing the thoracic cage. The soft structures are made up largely of the elements, carbon, oxygen, hydrogen and nitrogen; the bones of calcium; while sodium, potassium, magnesium, phosphorus and iron are present in the cells and fluids in small quantities. Each one of these elements has its own particular power of intercepting the rays

as they pass through, and the degree to which tissues will be visualized will depend on the relative quantities of elements of higher and lower atomic numbers which compose them.

The thicker any structure which absorbs rays the denser is its shadow. The shadow of edematous tissue should be more pronounced when many cells take part in the infiltration, and these cells, on the other hand, affect the shadows on the plate much less than fibrous tissue and calcareous deposits. But no matter what the shadow-casting power of a given tissue, the intensity of the shadow on the plate will vary with the thickness of the tissues responsible for it.

The relative capacity of the common elements found in the tissues of the chest for intercepting rays, according to the rule given above, taking hydrogen as 1, is as follows:

RELATIVE CAPACITY OF DIFFERENT ELEMENTS FOR INTERCEPTING ROENTGEN RAYS.

Element . . . H	C.	N	O	Na	Mg	P	K	Ca	Fe
Atomic No. . . 1	6	7	8	11	12	15	19	20	26
Capacity to intercept rays . 1	1296	2401	4096	14,641	20,736	50,625	130,321	160,000	445,976

From this table, it can be seen that the tissues which make up the soft structures offer comparatively little hindrance to the passage of the rays, while the alkalies and alkali earths, phosphorus and iron offer relatively greater obstruction. Ca, which is found in large quantities in bones and calcified nodes, casts very dense shadows.

The shadows on a plate will depend upon the aggregate of intercepted rays caused by the particular tissues superimposed on each other. To the extent that the relative quantity of the different elements in the tissues which intercept rays differ under conditions of health and disease, so the plate of the normal and pathologic lung will differ.

It is often taken for granted that pathologic structures are revealed in all instances, but nothing could be farther from the truth. Some are shown; others are not.

Assuming that the Roentgen rays are passing through the chest in such a manner that they will be intercepted in accordance with the fourth power of the atomic number of the elements entering into their composition, we can see that tissues containing large quantities of Ca, Fe, P and alkali earths would cast comparatively heavy shadows, while others made up of C, H, N and O, such as the ordinary protein material of the tissues would interfere but slightly

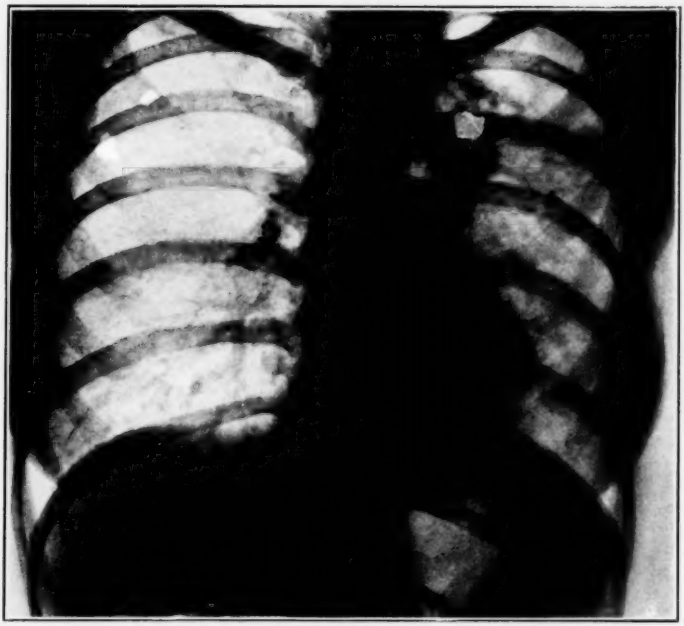

FIG. 1.—*Dorsoventral plate.* A large irregular cavity is seen near the left apex, with moderate exudative inflammation immediately below, and widespread scar and a lesser activity toward the base. Apparently little evidence of pleural involvement. Right lung emphysematous but practically free from disease.

FIG. 2.—*Ventrodorsal plate.* Cavity same as in Fig. 1. Much more extensive exudative infiltration below the cavity than shown in dorsoventral plate. Marked pleural haze over left hemithorax.

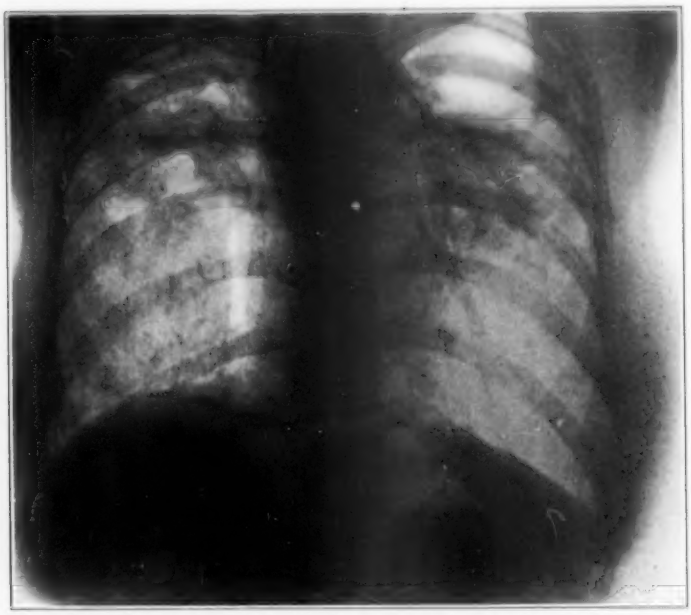

FIG. 3.—*Dorsoventral plate.* Large cavity in upper portion of left lung. Extensive fibrocaseous infiltration below to fourth rib. Right lung shows some tissue loss at apex. Fibrocaseous lesion in upper half. Slight pleural haze over left hemithorax.

FIG. 4.—*Ventrodorsal plate.* Large cavity occupying apex of left lung. Considerable fibrocaseous infiltration immediately below, more extensive and more active than shown in Fig. 3. Right lung also shows large fibrocaseous infiltration in the upper half of the lung, more extensive and more active than that shown in Fig. 3. Pleural haze over left hemithorax more marked than in Fig. 3.

and might hardly make an impression on the plate. This occurs in practice as has been pointed out by different observers. This inability of certain pathologic tissues to intercept rays because the elements which enter into their composition are of low atomic number, we accept as a limitation of the use of chest plates which cannot be overcome.

Error Due to Vertical Plane in which Chest Pathology is Found. Another serious source of error in chest plates arises from the depth of the chest through which the rays must pass and the fact that the pathologic foci lie in different vertical planes. The tube gives off both soft and hard rays at the same time and in order to make a plate that is sufficiently clear for interpretation the operator must give careful heed to the *penetration* of the rays. In order to visualize structures near the screen it is necessary to use rays which overpenetrate the tissues nearest the tube and *vice versa*.

In order to secure a true picture in which all parts of the lung would be equally represented, every vertical plane of the chest through which the rays pass would have to be exposed to rays of the same degree of hardness or softness. These conditions cannot be met in the application of Roentgen rays to the examination of the chest and therein lies certain very definite sources of error.

This source of error, however, can be overcome to a certain extent by taking plates both dorsoventrally and ventrodorsally. A plate taken dorsoventrally will show the structures in the anterior portion of the chest at the expense of those in the posterior. When the two are considered together the combined plates will come more nearly representing the actual lesions within the chest than that shown by plates taken in one direction alone; but even then, there must of necessity be certain areas which will not be properly visualized.

It is impossible to secure sufficient definition and detail in a cut to illustrate the small but very important differences which appear in some of the plates when taken both dorsoventrally and ventrodorsally. Particularly is this true in instances where the amount of infiltration is very limited. Therefore, I deem it much better to illustrate the point by plates taken of patients suffering from advanced tuberculosis, leaving it to each clinician to satisfy himself in his own practice in case of less extensive lesions.

The following cases with plates taken in both directions will bear out the assertions which are herein discussed.

Case 7277 (Fig. 1 and 2). The patient entered the sanatorium in March, 1926, at which time she had two small cavities in the left apex, an extensive active disease through the upper lobe and a slight involvement in the upper right. The disease become temporarily quiescent after a time, but nine months after beginning treatment, an extension of the disease took place in the neighborhood of the cavities, the tissue between them sloughed out, and the tissues below the cavity became the seat of an exudative process.

Physical examination revealed more active disease posteriorly than anteriorly and more than was indicated by the plate taken dorsoventrally. A ventrodorsal plate was then taken which gives us a truer picture of the condition, one which corresponds more nearly to the findings on physical examination. On comparing these two plates, Figs. 1 and 2, one would not recognize them as being of the same chest. The difference in both pulmonary and pleural shadows is very marked.

CASE 7877.—(Figs. 3 and 4.) The patient entered the sanatorium in July, 1922, at which time she had a double lesion with cavity in both apices. The cavity in the right side finally shrank and almost disappeared. That in the left enlarged greatly, extending from the apex to the second interspace, and the disease process in both upper lobes and a portion of the lower became very active. The patient showed poor resistance and at no time was she entirely free from symptoms for more than a few weeks at a time. In December, 1926 the disease began to show increased activity. The temperature became more elevated, toxic symptoms appeared, and cough and expectoration increased. Repeated examinations showed extensive activity in both lungs. The Roentgen ray plates taken dorsoventrally showed a gradual lessening in the lung shadows, but the patient continued to show toxic symptoms and loss of strength. Signs on auscultation at the base of the cavity anteriorly showed lessened activity but those posteriorly and in the upper half of the right lung were those of a very active process. The ventrodorsal plate revealed a much more extensive disease than was shown by the dorsoventral plate, both in the lung and in the pleura.

Summary. 1. The findings on physical and Roentgen ray examination of the lungs show some variation in nearly all instances, and in a small percentage the differences are very marked.

2. The ability of the disease process in the lung to produce shadows depends upon the power of the various elements making up the structures to intercept the rays, and this varies approximately according to the fourth power of the atomic number of their composing elements. Therefore, on the plate, small lesions may show perfectly if composed of elements whose atomic number is high, and large ones may not show at all if the atomic number of the chief component elements is low.

3. Lesions nearest the plate (taken at a distance of 40 inches) show best, because the tissues nearest the tube are overpenetrated and consequently fail to intercept the rays and produce shadow. Therefore, there is considerable variation in plates taken anteroposteriorly compared with those taken posteroanteriorly. If a small lesion lies near the surface of the chest wall nearest the tube, it may not be detected at all by the Roentgen ray. This error is lessened, but not eliminated, if the tube is some distance from the patient.

4. When small lesions are suspected on physical examination, the patient should be placed dorsoventrally if the lesion is suspected anteriorly, and ventrodorsally when suspected posteriorly, or, what is better, plates should be taken in both directions.

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PAROXYSMAL OCULOGYRIC CRISES IN PARKINSONIAN ENCEPHALITIS.*

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The presence of a lesion in the mesencephalon, resulting in the well-known eye disturbances of epidemic encephalitis, has always been considered the most important signal sign of the disease. To this have been added many associated eye signs due to further progression of the disease, mostly occurring in the acute stages, some of them eventually becoming chronic.

Recently there have appeared more and more references in the foreign literature to a new eye syndrome whose characteristics differ strikingly from the above, namely, that it appears late in the disease, perhaps preceded by no previous eye symptomatology, and almost invariably a sequel to the syndrome of Parkinson. I am referring to the syndrome of oculogyric crises of conjugate deviation of the eyes. These are paroxysmal in nature and appear without warning. It has been possible for me to observe a group of these cases during the past year, and there follows a short case history of the patients.

Case Reports. Case I.—M. L., male, aged twenty-four years, an electrician, gave no definite history of acute illness. He complained of eyes having rolled upward about two years ago, which occurred every other day for about two months, with drowsiness. During the past six months there has been a recurrence of eye movements with some headaches.

Physical examination showed slight nystagmus, upward and to the right. Pupils are small and do not react to light. There is the characteristic Parkinsonian rigidity with very slight tremor.

* Presented before the American Neurological Association, June, 1927.

The blood count was normal. The blood pressure was 110 systolic and 65 diastolic. Wassermann reaction on the blood and spinal fluid was negative. The spinal fluid showed three cells; globulin negative, colloidal gold curve, 112210.50000.

FIG. 1.—Case I. M. L. Shows upward turning movement of eye to left. Head to left, slightly upward.

FIG. 2.—Case II. I. B. Marked deviation of eyes to left and upward. Eyelids flutter. Head to left and upward.

CASE II.—I. B., aged twenty-seven years, had a severe attack of encephalitis in 1919, at which time she slept for three weeks, and was confined to

bed for a much longer time. In 1925 she noticed that movements became slower. Rigidity of posture and expression has progressed. About six months later she noticed onset of spasm of eye muscles which pulled her eyes up and to the left. There is rarely diplopia. The attacks occur two or three times a week, and last twenty minutes to eight hours. At times she has a feeling of air hunger and gasps.

Physical examination shows that the pupils are small and react sluggishly to light; there is no nystagmus. The facies is somewhat masked and she smiles easily. Parkinsonism is present to a moderate degree, and there is no tremor except on grip. Eye crises are accompanied by a fluttering of the eyelids, a turning movement to the left and upward with associated turning of the head and neck. Her blood pressure is 90 systolic and 50 disatolic. The blood count is normal. The blood chemistry is also normal. The Wassermann test on the blood and spinal fluid was negative. The spinal fluid showed no cells. The globulin was 1+ (red blood cells). The colloidal gold curve was 11.52210.50000.

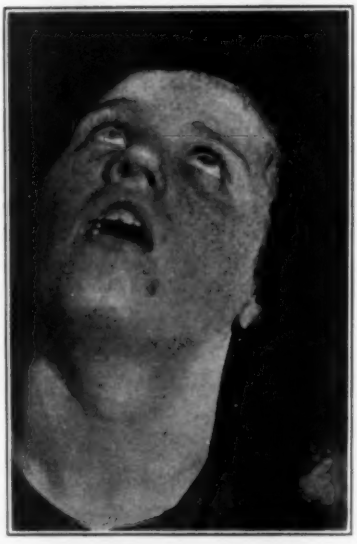

FIG. 3.—Case 3. A. M. Forced turning of head to right and backward with upward deviation of eyes. Marked Parkinsonism.

CASE III.—A. M., aged fourteen years, a schoolgirl, in February, 1923, had attack of encephalitis—diplopia being present; though she looked drowsy, she did not sleep until 2 A.M. It was never necessary for her to go to bed, and she slept very little. After the acute attack was over, there was slowing down of movements, indicating a beginning Parkinsonism. This has progressed, but has not prevented her from attending school. Because of the diplopia which remained and the abnormal posture of the head (turned to the right) an operation was done to correct both. Only partial relief was obtained from the diplopia by this operation. One year ago there appeared spasms of deviation of the eyes upward and to the right, lasting one-half to three-quarters of an hour, on an average of once a week, rarely every second day. Sometimes these attacks come and go.

Case IV.—I. A., aged thirteen years, in February, 1923, was admitted to St. Mary's Hospital for Children with an acute febrile attack of encephalitis. This began with choreiform movements, diplopia and lethargy. A spinal-fluid examination then showed 69 cells and a positive globulin. This was followed by a facial paralysis which cleared up and a subsequent Parkinsonian mask. She was afebrile in three weeks, and was discharged in a month, while six months later, when seen at my clinic, she had a well developed Parkinsonian syndrome with marked rigidity, almost limiting the movements in the left arm. She has a peculiar attitude, stooping to the

Fig. 4.—Case IV. I. A. Attack not in progress. Parkinsonism especially on left side; extension of fingers; facial mask with involuntary movement of tongue in progress.

left, with a gait almost dystonic in type. She snaps the fingers of the right hand, and has a tremor of the hands. The pupils react; the reflexes are greater on the right than on the left. In December, 1925, she first noticed that her eyes turned up too easily, but it was not until November, 1926, that paroxysmal conjugate deviation of the eyes became pronounced. The eyes turned upward to the left. Headache often preceded the crises. These have persisted until the present time, though much ameliorated by hyoscine. Other signs of note in this case have been occasional moods of hypomania with exhilaration and marked emotional storms and variability of mood. About six months ago, when standing, the patient started to sort of

hop up and down, as though trying to balance herself on the left leg. This, however, was quite rhythmical. At another time, there was a constant repeated spasm of the tongue; it kept moving about in the mouth and was protruded frequently.

Comment. The detailed report of 4 characteristic cases of oculogyric crises reveals that they have striking features in common. They all have the Parkinsonian syndrome; they have unquestionably had encephalitis; the attacks have come on at an interval of at least one year after the acute disease; the attacks are all conjugate eye deviation to the left and upward. Associated with this is usually a cephalogyric (head turning) torsion movement to the left and slightly upward.

A tabulation of the clinical variations which these cases present is of interest. In 2 of the cases the acute disease was in 1923; in another in 1919 and in another no history was obtained of such. The Parkinsonian syndrome began in 2 cases within three or four months after the acute disease, these same cases presenting their oculogyric crises three years after the acute onset. Another case whose Parkinsonism appeared six years after the acute disease had an appearance of the eye crises only six months later, while in the first case the paroxysmal eye crises appeared two years after the onset of the Parkinsonism. Therefore, from these cases we can draw no conclusions as to the severity of the disease, the early or late appearance of Parkinsonism, or of the attacks of conjugate deviation of the eyes. The variety of associated signs in these cases was considerable; diplopia, nystagmus, breathing episodes, torsion of head and neck, tongue spasms, emotional crises with euphoria, acute dystonic "hop," suggesting the dromedary gait while standing still.

The appearance of the spasms usually is noted in the afternoon, after playing cards, in a strong light, or after emotional disturbance, all stressing the effect of fatigue.

They are all definitely helped by the administration of hyoscin hydrobromid by mouth.

A review of the literature on these oculogyric crises reveals that 37 cases are recorded, some of them in detail, but most of them rather superficially. A marked variation in the signs which are found associated with these attacks is of particular importance in bringing to us a fuller conception of their possible etiology.

The spasms of conjugate deviation in all of my cases were to the left and upward. Many cases showed also a turning to the right and upward, a few just an upward movement with fixation and extension of the head, and a more rare case in which fixation occurred in the forward position. Again there are rare cases in which an alternation from left to right is seen, as reported by Popowa.[1] Some of these patients can at will turn their eyes down, and fix them anywhere, only to have them jump back again "as though on a

spring." Others cannot make any movement of the eyes throughout the duration of the paroxysm. A fluttering of the lids, a widening of the palpebral fissure, and a jerky upward turning movement of the eyes are not infrequent observations during the course of the crisis.

The symptomatology of the paroxysm may be associated with pain in or around the eyes and a feeling of heaviness in the forehead is commonly noted. There has been observed no loss of consciousness, but Wimmer[2] states that there is a slurring of consciousness, so that they are unable to answer questions. A distressed anxious attitude is observed at times which may be part of the associated vegetative disturbance, and the attack will sometimes terminate in sleep, most probably the expression of the great fatigue so frequently seen accompanying the disturbance. Marked emotional explosions, such as laughing and crying fits, are associated with this disturbance as part of the Parkinsonism.

Other physical signs which have been revealed are a diminished reaction to light and accommodation during the attack, and though an exaggeration of the conjugate deviation is observed, on testing the labyrinth on the same side, that on the opposite side shows a complete loss of the labyrinthine reaction.

The element of hypertonia which is so striking a sign in these cases is noted by Marinesco[3] by the association of a torsion of the body in the same direction as the deviation spasm. An extensor spasm of the lower extremity may be seen, and other bizarre attitudes are occasionally assumed. Here the similarity to such tonic postural syndromes as described by Mangus and de Kleijn[4] is interesting. According to the intensity of the hypertonia, Marinesco (and others) also notes vegetative symptoms, such as acceleration of the cardiac and respiratory rhythm, exaggeration of the oculocardiac reflex, and vasomotor and secretory disturbance.

The association and variety of symptoms and physical signs which serve to make up this syndrome of "tonic eye fits" (Wimmer) or oculogyric crises indicate that the lesion which produces them is merely part of a more widespread process throughout the basal ganglia, which, during some stage of its development, invades another associated nucleus or tract with the additional picture appearing.

The paroxysmal character of postencephalitic disorders is one of its most noteworthy variations from syndromes due to other organic nervous diseases. The rhythmical myoclonias, yawning attacks, variable types of forced breathing, paroxysmal sympathetic syndromes are examples of such disorders, many of which are entirely new pictures to us. To what must we attribute this feature? Are we to consider these cases of chronic epidemic encephalitis, according to Wimmer? Are they cyclical because they are fundamentally disorders in which the mesencephalic and striatal vegetative centers

are disturbed? Or perhaps there is an element in it of toxemia from some focus, such as the intestinal tract. Or are there some subtle biochemical changes which have taken place from the disease, resulting in the lowering of the threshold of inhibition and hyperkinesis appearing at moments of altered tone from calcium or other unknown chemical imbalance?

In general, it may be noted that hyperkinesis in its different aspects is the outstanding basis of this syndrome. These attacks are paroxysmal in type and due to an added hypertonic element. Wimmer has denoted them tonic eye fits, and said that they bear a relationship to the tonic phase of genuine epileptic attacks, while Lehrfeld has likened the spasm to the upward deviation of the eyeballs in cases of epilepsy. In addition, there is a fluttering of the lids and some of these cases have a postcritic sleep not unlike the epileptic. Kulkow[5] and Sterling[6] have suggested an analogy to an extrapyramidal epilepsy and the contribution of the neostriatum toward the epileptic seizure is still a matter for conclusive study.

Margulis and Model,[7] in a discussion of tonic convergence spasm, stress the part which the vestibular apparatus plays in this syndrome and note that the impulses from the labyrinth and vestibular nuclei through its postlongitudinal fasiculus connections are the chief regulators of the tonus of the visual apparatus, though they conclude that the influence of the striopallidal system in causing spasm of the associated eye muscles cannot be altogether excluded. These same writers find a center of convergence and independent center for lateral and vertical movements of the eyeball are located in the anterior corpora quadrigemina. In accord with these writers are Barré and Duverger.[8] However, the majority of writers consider that the problem is more complex.

Paulian[9] considers the question as to whether these attitudes are due to disturbance in the cerebellum. Lowering and throwing back of the head would seem more closely connected with the pathology of the vermis and point to destruction or excitation of a zone localized in this region or its peduncle. This is in line with the tendency to orientate within that organ phenomena formerly located in the central nuclei.

It would seem that the localization of the lesion in these oculogyric crises could be placed very definitely outside of the cerebellum and vestibular paths, for why should these attacks occur only in Parkinsonian cases associated with hyperkinesias? For at the moment these are positively referable to the basal nuclei.

Before concluding this discussion, a brief mention of the paper presented before this Association by Brock and Wechsler,[10] in which they pointed out that there is a loss of the righting reflex ("stellreflexe" of Magnus-de Klijn) in Parkinsonism should be made. They quote Magnus as emphasizing that the midbrain and interbrain region contain the centers concerned in the reflex postural

adjustments. Without presuming to make a definite parallel, the occurrence of conjugate deviation of the eyes in crises associated with a cephalogyric movement and frequently torsion or extension of the limbs to the side of the eye deviation are probably allied to the Magnus and de Klijn postural reflexes of a similar type.

It is, therefore, the conclusion of most of the observers of this syndrome that we are dealing with an extrapyramidal phenomenon due to a subcortical localization. Lemos, Fischer,[11] Popowa, Kulkow, Bing and Schwartz,[12] Stein,[13] Barkas,[14] Wimmer, Marinesco[15] and others have all stressed this point with minor variations. Diminished regulation by the neostriatum results in subcortical automatisms—a "release" phenomenon explaining the paroxysmal nature and the quadrigeminal tubercles through the neostriatum, its physiopathologic genesis according to Bing and Schwartz. Marinesco and others state that the accumulation of metabolic products due to fatigue (or infection, intestinal, etc., if I may add) may paralyze the inhibition upon the tone-genetic centers. Thus commences an attack of hypertonia. An excitation of the posterior longitudinal bundles is considered a possibility by these authors. Wimmer, after a thorough discussion of the above theories, concludes that "tonic eye fits" are derived from a peripheral extrastriatal irritation and not primarily from a striatal lesion.

Conclusions. A logical deduction from the characteristic features of this unusual syndrome seems to me to be as follows:

1. That paroxysmal oculogyric crises are an episode in the course of a hyperkinetic phenomenon, as instanced by the presence of associated hypertonias, Parkinsonism, torsion spasms, and so forth.

2. Hyperkinesis is a subcortical striatal extrapyramidal mechanism.

3. Conjugate deviation of the eyes would seem to be dependent upon a posterior longitudinal fasciculus—anterior corpora quadrigemina complex.

4. The hypertonic paroxysms of conjugate deviation resulting in forced movements upward frequently accompanied by other torsion phenomena would ally these two mechanisms and suggest a striatal, quadrigeminal body—posterior longitudinal fasciculus complex as the ultimate physiopathologic genesis.

5. The etiologic factor is, of course, a more chronic stage of epidemic encephalitis. The immediate cause of the paroxysms is perhaps fatigue, emotion, metabolic accumulations, focal absorption, and so forth.

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REVIEWS.

THE TONGUE AND ITS DISEASES. By DUNCAN C. L. FITZWILLIAMS, C.M.G., M.D., CH.M., F.R.C.S. (EDIN. and ENG.). Pp. 505; 166 illustrations. New York: Oxford University Press, American Branch, 1927.

THE author has given to the profession a very exhaustive treatise on a subject that has been more or less neglected in the last few years. This book of 505 pages covers diseases of the tongue in all phases. One of the chief lessons, and perhaps *the* chief lesson, to be obtained from perusal of its pages, is that cancer of the tongue is curable, provided it is recognized early. Such early recognition can be only brought to the notice of members of the profession by a book of this sort. It is their business to transmit such necessary information to the public. Such men as Clarke, Butlin and Spencer did wonderful pioneer work in this branch of surgery. The author attempts to continue and to advance their contributions. The illustrations are numerous and in most respects well chosen. A feature of the work that is specially pleasing is the recounting of case histories in great numbers illustrative of the subject under discussion at that particular time. Many interesting features in comparative anatomy and pathology are presented. The bibliography is thorough and up to date. Every feature of the tongue and its diseases is considered. Cancer is given particular attention having five chapters devoted to its discussion. The chapter on the operative treatment could be a little fuller and better illustrated. This latter is the only adverse criticism offered by the reviewer. E. E.

AN INTRODUCTORY COURSE IN OPHTHALMIC OPTICS. By ALFRED COWAN, M.D. First edition. Pp. 262; 121 illustrations. Philadelphia: F. A. Davis Company, 1927. Price, $3.50.

TWO distinct contributions have been made by the publication of this book. It has been shown that the complicated dioptrics of the eye can be explained on the Gaussian theory by a system of construction, employing only the simplest arithmetic and easy algebraic formulæ. Further, the presentation is so clear, with so

many illustrative examples, that what has been a bugbear in the past to those having no inherited love for mathematics becomes a pleasure in the reading.

The book is profusely illustrated with figures, many in colors, which makes the lines in the constructions easy to follow.

To all those who have an interest in lens systems and more particularly as this applies to the eye, this book will be a very welcome possession. F. A.

FEEDING AND THE NUTRITIONAL DISORDERS IN INFANCY AND CHILDHOOD. By JULIUS H. HESS, M.D., Professor and Head of the Department of Pediatrics, University of Illinois College of Medicine. Fifth revised and enlarged edition. Pp. 566; 45 engravings in the text and one full-page colored plate. Philadelphia: F. A. Davis Company, 1927. Price, $4.50.

THE popularity of this text is evidenced by the frequency with which new editions appear, this last within two years. Its favorable reception is due to its universal appeal, to students, interns, practitioners and pediatrists. Practically everything of value in infant feeding and nutrition is to be found in this book, explained in sufficient detail for the specialist, yet not too technical for the student to grasp. The system of normal feeding is definite and scientific, the indications for special foods are explicitly stated, and the steps in the management of nutritional disorders are clearly outlined. The most recent advances in this field of pediatrics have been included in the new edition. More tables and formulæ have been added, and the whole group rearranged. The reviewer gives this work his whole-hearted recommendation and can assure the purchaser that his money will be well spent. J. S.

DISEASES OF THE NEWBORN: A Textbook for Students and Practitioners. By JAMES BURNET, M.A., M.D., F.R.C.P. (EDIN.), Lecturer on Diseases of Children, School of Medicine of the Royal Colleges, Edinburgh. Pp. 275. New York: Oxford University Press, American Branch, 1927.

A WELL arranged manual of the commoner affections of the newborn period. Expressly intended for the student and practitioner, the conciseness of the text is commendable. The author is frankly hostile to routine circumcision and to the use of long-feeding intervals in the newborn. Little space is given to the inauguration of artificial feeding where this is necessary in the newborn infant. The reviewer feels that brevity has been attained often at the expense of completeness, especially in the field of therapeutics.

J. S.

THE DIAGNOSIS OF PANCREATIC DISEASE. By ROBERT COOPE, M.D., B.Sc., M.R.C.P., Senior Assistant Physician, Royal Southern Hospital, Liverpool; Assistant Physician, Hospital for Consumption and Diseases of the Chest, Liverpool; Lecturer in Clinical Chemistry, University of Liverpool. Pp. 112; 12 illustrations. Edinburgh: Oxford University Press, 1927.

THIS little book covers in a brief but most satisfying way the important established facts regarding the anatomy, physiology and pathology of the pancreas, as well as the clinical aspects of its disturbances. The various tests for pancreatic function that have been proposed are discussed and evaluated. A considerable bibliography is included. While it presents no new data it will be found of decided help to anyone wishing a brief statement of our knowledge regarding diseases of the pancreas and a guide to the original literature. T. M.

DISEASES OF THE MOUTH. By STERLING V. MEAD, D.D.S. Professor of Oral Surgery and Diseases of the Mouth, Georgetown Dental School; Professor of Diseases of the Mouth, Georgetown Medical School, etc., Washington, D. C. Pp. 578; 274 original illustrations and 29 color plates. St. Louis: C. V. Mosby Company, 1927. Price, $10.00.

THIS is the most comprehensive work that has yet appeared in one volume on this subject in America. The author discusses all of the diseases manifesting themselves within the mouth, whether medical, surgical, or purely dental, and naturally falls short of adequate presentation in the limited space allotted. The sections relating to dental caries, diseases of the dental pulp, irregularities of the teeth, etc., could well have been omitted, since they are more properly and completely dealt with in works on operative dentistry and orthodontia. One fails to see the reason for the differentiation of ulceromembranous gingivitis and Vincent's stomatitis. The classification of odontoma as a connective tissue tumor is open to question. The recommended application of silver nitrate to leukoplakia patches is not in accord with accepted methods of treatment. Recent fractures of the mandible should not be treated by direct fixation with bone sutures. A second edition should eliminate several typographical errors, especially in references to proper names. The illustrations and colored plates, with few exceptions, are extremely helpful in clarifying the text.

The book can be recommended to the physician as presenting a sound dental viewpoint of oral infection in its bearing upon the health of the body as a whole. R. I.

THE EAR, NOSE AND THROAT IN GENERAL PRACTICE. By D. A. CROW, M.B., CH.B. (EDIN.), Otolaryngologist to the Royal Sussex County Hospital, Brighton, the Sussex Throat and Ear Hospital, etc. Pp. 150; 45 illustrations. New York: Oxford University Press, American Branch, 1927.

THIS book was written for the general practitioner by one who has spent ten years in general practice before specializing, and the author goes rather deeply into the history, symptoms, and his method of examination of the nose, throat and ear.

Early paracentesis, and method of performance on the acute ear is greatly stressed to prevent deafness later in life. The acute ear and mastoid operation are touched upon superficially, but they give the general practitioner a good idea as to treatment and indications for operation.

The tonsil operation is taken up in detail, with the author's method, which is seldom used in this country. There are many good points that the general practioner can get by reading this little book. D. H.

THE LIFE AND WORK OF SIR PATRICK MANSON. By PHILIP H. MANSON-BAHR, D.S.O., M.D., F.R.C.P., and A. ALCOCK, C.I.E., LL.D. (ABERD.), F.R.S. Pp. 273; 12 illustrations. New York: William Wood & Co., 1927. Price, $5.50.

SOME think that the chief credit for medical discoveries that greatly benefit mankind should go to the man making the actual practical discovery; others, to him or those who have made the more recondite or theoretical underlying advances; still others grant that there is sufficient credit available for both types without making invidious distinctions; while there are probably some who think the allocation of credit not worth bothering about at all. To all but the latter group, but especially to those medical men in the second category, Sir Patrick Manson's work will stand out prominently in the crowded story of the previous generation. This sympathetic account by his son-in-law, written with the help of Colonel Alcock, tells both the biographical and scientific tale in such a charming way that the book should have a real success even with the competition that must be expected in these biographical days.

Born in Scotland of old Norwegian stock, Manson spent half his life in China (where he did his important filaria work), came to London in the plenitude of his powers (there achieving his masterpiece—the formulation of his theory of the mosquito transmission of malaria), retired to Ireland in 1912 and died there in 1922. Each phase of this internationalism gets proportionate treatment in the book under review, and, in addition, one gets a clear picture of the philosophy of life of a courteous gentleman who "warmed both hands before the fire of life." E. K.

THE ESSENTIALS OF OTOLOGY. By GEORGE BIRMINGHAM MCAULIFFE, A.M., M.D., F.A.C.S. Assistant Professor of Otology, Cornell Medical College; Oculist and Aurist, Misericordia Hospital; Consulting Aurist, Waterbury and Southampton Hospitals; Aurist to the School for the Deaf, New York City; Chief of the Ear Clinic, Cornell Dispensary. Pp. 172; 46 illustrations. New York: Oxford University Press, American Branch, 1927.

AN excellent book on otology for undergraduate medical students that gives in detail the methods of examination of the external ear and drumhead, with fine illustrations. Diseases and treatment of the canal, middle ear and operative technique of the mastoids are so simplified and illustrated that a student in otology will have little difficulty in grasping. A small chapter devoted to hearing and complications following mastoid operations is well written. The anatomy and physiology is left to the end so as not to confuse the student. The book is well written and should be of great help to undergraduate medical students in otology. D. H.

THE CARRIER PROBLEM. By K. C. PAUL, M.B., B.S., Some-time Research Student in Medicine, University of Madras; with FOREWORD by DAVID NABARRO, M.D., F.R.C.P., Director of Research and Pathologic Laboratories, The Hospital for Sick Children, London. Pp. 102. London: Oxford University Press, American Branch, 1926. Price, $1.75.

THIS little volume presents in a concise manner the more important facts concerning "carriers." There are ten chapters, each dealing with a special disease. Among the subjects treated are carriers of enteric, meningococcal, pneumococcal, streptococcal infections. Diphtheria, acute poliomyelitis, bacillary and amœbic dysentery and cholera are also discussed. The treatise is far from being complete, but does contain much that is useful and instructive. J. S.

GONOCOCCAL INFECTION IN THE MALE. By ABRAHAM L. WOLBARST, M.D., Urologist and Director of Urologic Clinics, Beth Israel Hospital; Consulting Urologist, Central Islip State Hospital, Manhattan State Hospital, and Jewish Memorial Hopital. Pp. 224; 82 illustrations, 7 colored plates. St. Louis, Mo.: The C. V. Mosby Company, 1927. Price, $5.50.

THE author, with the needs of the general practitioner in view, has written a clear and concise book upon gonorrhea in the male. He has recorded the present-day methods of diagnosis and treatment,

which are based upon a wide personal experience. He emphasizes the fact that gonorrhea is a pathologic entity, worthy of our most serious study and that gentleness rather than vigor in therapeutic attack is the keynote to successful results. Though the book adds but little which is new, it does summarize the concept of this disease in such a way that it is easily grasped. The general practitioner who wants to quickly find and refresh himself upon the diagnosis and treatment of acute and chronic gonorrhea, will find this book a perfectly safe guide. A diverting chapter has been added, "Views on Gonorrhea," by J. E. R. McDonagh, of London, England, without apparent reason other than a friendly *beau geste*. In a confusing way it conveys the *unusual* theories and treatments (together with a little advertising of drug houses) of this one physician.

A. R.

DISEASE PREVENTION. By HERBERT H. WAITE, M.D., Professor of Bacteriology and Pathology, University of Nebraska. Pp. 667. New York: Thomas Y. Crowell Company, 1926. Price, $4.50.

THIS volume represents a useful compilation of the essential practices in modern methods of disease prevention. The inclusion of historical material tracing the development of these methods adds greatly in arousing the reader's attention. According to the author, the book is "primarily intended for social workers, state and municipal officials, hospital workers and all those who are engaged in the highly laudable work of combating disease."

J. S.

BOOKS RECEIVED.

New Books.

Ars Medici. The Journal of the American Medical Association of Vienna. Reviews and Abstracts of all Branches of Foreign Medical Literature. Edited by DR. M. OSTERMANN. Volume V, 1927. Pp. 592. Published monthly in Vienna. Price, $3.30. Abstracts of numerous articles arranged according to the specialties together with a reference index, subject and author. Appearing annually since 1923.

The Abdominal Surgery of Children. By L. E. BARRINGTON-WARD, CH.M., F.R.C.S. (EDIN.), F.R.C.S. (ENG.). Pp. 283; 82 illustrations. New York: Oxford University Press, American Branch, 1928. Price, $4.50.*

Mongolism. By KATE BROUSSEAU and H. G. BRAINERD, M.D. Pp. 203; 47 illustrations. Baltimore: Williams & Wilkins Company, 1928. Price, $4.50.*

Reviews of titles followed by an asterisk will appear in a later number.

Stammering. By ISADOR H. CORIAT, M.D. Pp. 68. New York and Washington: Nervous and Mental Disease Publishing Company, 1927.*

Special Cytology. Edited by EDMUND V. COWDRY. 2 volumes. Pp. 1348; 693 illustrations. New York: Paul B. Hoeber, Inc., 1928.*

Food Infections and Food Intoxications. By SAMUEL REED DAMON. Pp. 264; 25 illustrations. Baltimore: Williams & Wilkins Company, 1928. Price, $4.00.*

Local Anesthesia. By GEZA DE TAKATS, M.D., M.S. Pp. 221; 117 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price, $4.00.*

Clinical Surgery: An Introduction for Junior Students. By J. W. DOWDEN, M.B., F.R.C.S.E. Pp. 68. Edinburgh and London: Oliver & Boyd, 1928.

Antenatal and Postnatal Child Hygiene. By W. M. FELDMAN. Pp. 743; 175 illustrations. London: John Bale, Sons & Danielsson, Ltd., 1928. Price, $7.00.*

Centenary Number. The Glasgow Medical Journal, February, 1928. Pp. 224. Glasgow: Alex MacDougall, 1928. An interesting historical record of Glasgow and British medicine and medical journalism one hundred years ago.

Childbirth: An Outline of its Essential Features and the Art of its Management. Pp. 300; 23 illustrations. Chicago: University of Chicago Press, 1928.

Elements of Physiology. By ERNEST G. MARTIN, PH.D., and FRANK W. WEYMOUTH, PH.D. Pp. 784; 133 illustrations. Philadelphia: Lea & Febiger, 1928. Price, $8.00.*

Medical Clinics of North America. Tulane University Number, March, 1928. Pp. 261; 35 illustrations. Philadelphia: W. B. Saunders Company, 1928.

Les Associations Microbiennes. Leurs Applications Thérapeutique. By G. PAPACOSTAS and J. GATE. Pp. 438. Paris: Gaston Doin et Cie, 1928.

Progressive Medicine. Edited by HOBART AMORY HARE. Vol. I, March, 1928. Pp. 282; illustrated. Philadelphia: Lea & Febiger, 1928.

Asthma: Its Diagnosis and Treatment. By WILLIAM S. THOMAS, M.D. Pp. 279; 26 illustrations. New York: Paul B. Hoeber, Inc., 1928. Price, $7.50.*

Transactions of the American Otological Society, May 21 and 22, 1927. Vol. XVII, Part III. Pp. 244; illustrated. New Bedford, Mass.: By the Society, Reynolds Printing Company, 1927.

Reviews of titles followed by an asterisk will appear in a later number.

Aluminum Compounds in Food. By ERNEST ELLSWORTH SMITH, PH.D., M.D. Pp. 378. New York: Paul B. Hoeber, Inc., 1928. Price, $7.00. A digest of studies relating to the presence and effects of compounds of aluminum in food, including some unpublished researches of the author and other investigators, and a résumé of the investigations of the Referee Board of the United States Government.

The Surgical Treatment of Malignant Disease. By SIR HOLBURT J. WARING, M.S., M.B., B.Sc. (LOND.). Pp. 667; 296 illustrations. New York: Oxford University Press, American Branch, 1928. Price, $15.00.*

Strabismus. Its Etiology and Treatment. By OSCAR WILKINSON, A.M., M.D., D.Sc. Pp. 240; 120 illustrations. St. Louis: C. V. Mosby Company, 1927. Price, $10.00.*

New Editions.

Diseases of the Intestines, Liver, Pancreas, Gall-bladder, Etc. By ANTHONY BASSLER, M.D., F.A.C.P. Pp. 905; 277 illustrations. Third edition. Philadelphia: F. A. Davis Company, 1928. Price, $9.00.

Practical Dietetics for Adults and Children in Health and Disease. by SANFORD BLUM, A.B., M.S., M.D. Third edition. Pp. 280. Philadelphia: F. A. Davis Company, 1928. Price, $4.00. With numerous additions and alterations in calories, diabetes, hypertension, cancer, etc.

Modern Methods in the Treatment of Renal Disease. By HUGH MACLEAN, M.D., D.Sc., F.R.C.P. Third edition. Pp. 135; 8 illustrations. Philadelphia: Lea & Febiger, 1928. Price, $2.75. This is the third and enlarged edition of a well-known monograph, giving a short account of some of the newer methods employed in investigating renal function.

Diabetes: Its Treatment by Insulin and Diet. By ORLANDO H. PETTY, A.M., M.D., F.A.C.P. Pp. 153. Fourth edition. Philadelphia: F. A. Davis Company, 1928. Price, $2.00. Four editions in four years speak for themselves.

Physical Diagnosis. By W. D. ROSE, M.D. Pp. 819; 313 illustrations. Fifth edition. St. Louis: C. V. Mosby Company, 1928. Price, $10.00. The pathologic physiology of the heart and the manifestations of incipient cardiac insufficiency have been stressed in this edition.

Postmortem Appearances. By JOAN M. ROSS, M.D., B.S., M.R.C.S. Pp. 225. Second edition. New York: Oxford University Press, American Branch, 1928. Price, $2.50.

Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Passive Immunization against Scarlet Fever.—JAMES (*Lancet*, 1928, i, 227) writes that it is possible to immunize against scarlet fever with scarlet fever antitoxin. This is of particular value when the disease breaks out in institutions. The question, of course, of the amount of antitoxin necessary to produce immunity is answered by the employment of the Dick test. He found that immunity lasts from seven to ten days, as shown by a negative Dick, and can be at times produced by giving 10 cc. of unconcentrated serum or 2.5 cc. of the concentrated serum. He believes that it is wise to know the antitoxic strength of the serum, but failing this to give a dose of 5 cc. of concentrated scarlet fever antitoxin.

Experimental Typhoid Fever Induced in Guinea Pig with in Vivo Prepared Bacillus Typhosus Toxic Product.—HARRIS (*Proc. Soc. Exper. Biol. and Med.*, 1928, **25**, 372) has prepared a toxic product from Bacillus typhosus which when injected into guinea pigs gives a pathologic picture of the true typhoid fever. The method of preparing the toxin product consisted of introducing Bacillus typhosus which caused a peritonitis, filtering the resulting exudate after killing the animals, by passing through a Berkefeld letter N filter. Several injections were given to each experimental animal from two- to four-day intervals. Following these injections there was a rise in temperature and a marked leukopenia. Death occurred in from two to four weeks. At autopsy the changes in the reticuloendothelial system in a person dead from typhoid fever were found. Microscopic study of the lymphoid structures of the peritoneal cavity, including Peyer's patches, showed that pronounced pathologic alterations had occurred and many endothelial phagocytic cells were found. By this so-called *in vivo* method a bacterial-free toxic substance has been produced, which when injected into a guinea pig has much the same effect on the tissues as does the typhoid bacillus in the human.

SURGERY

UNDER THE CHARGE OF

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Acute Intestinal Obstruction.—MOORE (*Rhode Island Med. J.*, 1927, **10**, 123) claims that there is no known method of combating the late symptoms of the toxemia of acute intestinal obstruction. The percentage of cases resulting from recent postoperative adhesions is small. The high mortality rate can only be reduced by earlier diagnosis and operation. Clinically acute intestinal obstruction may be divided into two groups—simple obstructions with normal blood supply in the obstructed loop and strangulations, in which there is interference with the blood supply to the obstructed loop. In practice there appears to be another group which may be classified as a subgroup under simple obstructions and strangulations. These patients have complete obstruction to the passage of feces from the onset of symptoms, but gas escapes past the site of obstruction during the early hours or even days of obstruction. Complete obstruction to feces and gas eventually occurs either with or without strangulation. The distinguishing feature of these cases is their surprisingly good condition, considering the reported duration of obstruction. According to statistics of the author's series of cases, operations for acute intestinal obstruction during the first twenty-four hours of symptoms resulted in the highest percentage of recoveries. The author's experience with enterostomy in acute obstruction has been confined largely to the extremely toxic cases with a mortality rate of 67 per cent. The value, however, of enterostomy in acute obstruction is at present unquestioned if properly safeguarded to prevent excessive drainage. There is a wider acceptance of this operation not only in the late cases of intestinal obstruction, but in the earlier cases and in peritonitis also.

Complete Gastrectomy for Chronic Ulcer.—BUTLER (*Brit. J. Surg.*, 1927, **15**, 316) finds that the loss of the stomach as a machine for mixing, churning and softening food before it enters the small intestine is apparently not a very serious matter, but the loss of the stomach secretions with their power of sterilization is of much greater importance. The consequent invasion of the duodenum with pathogenic strains of bacteria often leads to ascending infection of the biliary passages. So far as the actual digestion of food is concerned, the patient appears to have no difficulty with either starch or muscle, but fat is in excess in the stools, though not to any serious degree. As it is almost all in the form of split fat, it is not likely to be due to pancreatic inefficiency.

THERAPEUTICS

UNDER THE CHARGE OF

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Liver Extract in Pernicious Anemia.—Following directly along the lines worked out by Minot and Murphy and by Cohn, a liver extract has been prepared which seems nearly identical with that employed by these investigators. This extract represents from 400 to 500 gm. of fresh liver in each 7.5 gm. of the dry powder or in 80 cc. of the liquid preparation. SEYDERHELM and OPITZ (*Klin. Wchnschr.*, 1928, **7**, 205) have employed this extract in a series of well-controlled cases of pernicious anemia in order to compare its efficiency with that of the administration of raw or cooked liver. The results of the investigation show it to be fully as effective as the liver diet, and owing to its rather pleasant taste its use sometimes seems possible in patients who rebel against the continued consumption of large quantities of liver, or whose digestion is upset thereby. In the course of the investigations the authors observed one patient in whom a preceding achlorhydria was replaced after three weeks' employment of the liver extract by the reappearance of free hydrochloric acid in the gastric juice. Simultaneously the gastric contents were found to be sterile, whereas previously Bacillus coli had been recovered abundantly in culture of the gastric juice. Whether this return of acid secretion was a mere incident has not yet been determined.

The Treatment of Chronic Bronchitis with or without Secondary Asthma.—The host of remedies advocated for the treatment of chronic bronchitis is in itself indicative of the fact that none of them is very trustworthy. VEILCHENBLAU (*München. med. Wchnschr.*, 1928, **75**, 222) recognizes this fact in his report upon the successful treatment of a small group of such patients by means of the intravenous administration of sodium cacodylate. He observed his best results by employing a 50 per cent solution which he injected at intervals of three days in doses beginning with 1 cc. and increased by this same amount up to 6 cc., at which point the daily dose is reduced by 1 cc. until the initial dose is again reached. He believes the mechanism of this procedure to depend mainly upon a partial sterilization of the lungs as a result of the excretion through them of decomposition products containing arsenic. There is also some evidence of an improvement in the elasticity of the lung through the direct action of arsenic. The treatment seems to be useless in spasmodic asthma, its effect being limited to that form which is immediately dependent upon the existence of chronic lung infection.

PEDIATRICS

UNDER THE CHARGE OF

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Prevention and Treatment of Asphyxia in the Newborn.—HENDERSON (*J. Am. Med. Assn.*, 1928, **90**, 583) contends that failure of the newborn to breathe or the condition of insufficient natural respiration should not be treated by the old-fashioned methods of skin stimulation. He feels that they are ineffective as well as unphysiologic and harmful. Resuscitation of the newborn should be based on the modern conception of the regulation of respiration by the action of the blood gases on the respiratory center. Oxygen is not a stimulant but a foodstuff. Deficiency of oxygen, beyond a first slight stimulating effect, depresses the nerve centers. In the absence of oxygen the tissues of the body cannot produce carbon dioxid. It is the carbon dioxid carried by the blood from the tissues to the brain that is the physiologic stimulant of respiration. When the center is depressed it requires more than the normal amount to produce activity. In the newborn the difficulty arises from compression of the head during labor and decrease of the blood supply to the brain thereby. In order to start respiration a gentle inflation with oxygen and carbon dioxid for two or three seconds, three or four times a minute, is recommended. As soon as natural breathing develops the inflations should cease, but inhalations of the oxygen-carbon-dioxid mixture should be continued until full respiration is established.

Intensive Postural Rest in the Treatment of Pulmonary Tuberculosis.—GEKLER and WEIGEL (*J. Am. Med. Assn.*, 1928, **90**, 590) believe that intensive postural rest, as they apply it, is the best method of treatment of pulmonary tuberculosis, ranking with artificial pneumothorax and thoracoplasty in value and effectiveness. This method of treatment is applicable in a wider range of cases. Complications are not more frequent and certainly less dangerous than with pneumothorax and thoracoplasty. When results are not obtainable the other two methods may still be used. Very striking benefits of this treatment are seen. The authors found the maximum amount of healing in view of the nature and extent of the lesions in fully one-fourth of their cases, and in another fourth there was considerable improvement. When clinical cures are obtained with postural rest they are just as lasting as with any other form of treatment.

The Urinary Leukocyte Count in Children in Normal and Pathologic Conditions.—FRIEDMAN and MITCHEL (*Am. J. Dis. Child.*, 1928, **35**, 201) found that the urine of apparently healthy infants and children contained an average of 10 pus cells per cubic millimeter, 90 per cent of the urine showed 20 cells or less, the upper limit for all ages was forty and the counts of 20 to 40 were present usually in girls of the older age groups. The urine of infants and children suffering from various respi-

ratory, intestinal or other infections often showed a varying of pyuria in excess of the normal. In cases of pyelitis and nephritis the counts were definitely higher than in other conditions that were studied. Leukocyte counts in the urine which showed more than 20 but less than 40 cells per cubic millimeter were suggestive of urinary infections, but this count may be found in concentrated urine and in acute febrile diseases. Leukocyte counts of over 40 per cubic millimeter are strongly suggestive of infection somewhere along the urinary tract if vaginitis is included. When large amounts of pus appear in the urine the diagnosis is obvious but in early or doubtful cases the estimation of the number of cells is often of the greater value.

The Effect of Thyroid Therapy on Children.—TOPPER and COHEN (*Am. J. Dis. Child.*, 1928, **35**, 205) studied the effect of thyroid therapy in 8 ward cases and 6 dispensary cases. In 4 children this subnormal thyroid activity, as evidenced by a subnormal basal metabolism and clinical manifestations of hypothyroidism, thyroid in small or moderate doses promptly brought the basal metabolism to normal, where it remained even after the thyroid administration was discontinued. In 1 child with a normal metabolism 12 gr. of thyroid extract by mouth combined with 5 mg. of thyroxin caused a transient increase in pulse and basal metabolism. In this case the combined dosage was in excess of that required for clinical benefit. In 9 children with normal basal metabolic rate as much as 15 gr. of thyroid extract daily did not increase the basal metabolism, but 4 of these children whose measurements were carefully followed showed a remarkable increase in growth during this period. Since thyroid extract in relatively large doses does not seem to have any effect on the basal metabolism of normal children, the stimulative effect on their growth leads to the question as to whether the basal metabolism should be a guide of thyroid therapy in normal children, especially as thyroid produces other physiologic and metabolic results.

Autopyotherapy of Empyema of Infants.—FLESCH (*Monatschr. f. Kinderh.*, 1927, **37**, 149) cured a case of empyema by resorting to Maki's method of injecting subcutaneously pus which had been withdrawn from a suppurating focus. In this case the whole right pleural cavity was filled with pus and the child's condition was very bad. Thirteen punctures were made at intervals of four to six days over a period of eight weeks, and each time from 0.25 to 1 cc. of pus was injected into the back; complete recovery ensued without any other treatment. In another case 9 treatments in a period of five weeks resulted in a complete cure.

Enuresis.—CALVIN (*J. Am. Med. Assn.*, 1928, **90**, 820) emphasizes that enuresis is really only a symptom and not a disease entity, and that it is usually a functional disturbance, the psychologic causes of which may vary considerably in different instances. In order to obtain successful results each case requires individual analysis. The method that cures one child may aggravate the condition in another. Punishment and fright may occasionally succeed for the time being but at the same time may do harm in other directions. Where the child is indifferent, lazy, slovenly and indolent his attention must be focused on the bad habit in order to cure him.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Tryparsamid: A Review of the Literature.—*Historical.* Tryparsamid was originally synthesized by JACOBS and HEIDELBERGER (*J. Am. Chem. Soc.*, 1917, **41**, 1581; *J. Exper. Med.*, 1919, **30**, 411). It was studied by BROWN and PEARCE (*J. Am. Med. Assn.*, 1923, **80**, 1521) in 1915, and the first publications concerning its properties appeared in November, 1919. This same year and again in 1920 clinical investigations were started in both trypanosomiasis and syphilis. BROWN and PEARCE (*J. Am. Med. Assn.*, 1924, **82**, 5), in a series of animal experimentations with tryparsamid discovered that the animals treated improved in general appearance and showed a marked gain in weight and energy. They also found that large doses of the drug could be given without evidence of intoxication, and that when intoxication did appear the animals recovered rapidly and completely. This evidence indicated that the drug probably did not produce serious depressions of vital processes and, therefore, could be employed without danger in this respect. Furthermore, their animals developed an apparent tolerance for tryparsamid, and the dose could gradually be raised beyond what was originally found to be a fatal one. It was at this time, however, that these authors noted the development of amblyopia in many of their treated animals. This complication evidenced by a drug which had very little spirillicidal power (Brown and Pearce) was sufficient reason for holding tryparsamid in an experimental state. Considering, however, its arsenic content (25.32 per cent), its apparent tonic properties, and its high degree of penetrability for the nervous system, further and more complete investigations were warranted, and from this time tryparsamid was carefully studied by many noteworthy investigators until the drug was finally given an eminent position in the armamentaria of the present-day syphilotherapist.

Action. According to VOEGTLIN and others (*Pub. Health Repts.*, 1923, **38**, 1003), Brown and Pearce, Fordyce and Rosen, and others, tryparsamid was found to have a high degree of penetrability for the nervous system. It reinforces the processes of natural resistance (Brown and Pearce). It has a relatively powerful trypanocidal action but little spirillicidal action (STOKES and WILHELM: *Arch. Dermat. and Syph.*, 1925, **11**, 579). The drug is a great tonic (HADEN and WILSON: *J. Am. Med. Assn.*, 1927, **88**, 473). It does not appear to attack the Spirochæta pallida directly as evidenced by the low therapeutic index

of 1 to 1 to 1 to 2 as compared with 1 to 7 to 1 to 10 for arsphenamin (Brown and Pearce).

Chemistry. Tryparsamid, synthesized by Jacobs and Heidelberger, is the sodium salt of N-phenylglycineamid-p-arsonic acid. It contains 25.32 per cent of arsenic; according to Stokes and Wilhelm, the arsenical content of a single dose is enormous (237 to 245 mg.).

Dosage and Administration. Tryparsamid is best given in doses of 1 to 4 gm., with an average of 2 to 3 gm., according to PEARCE (*J. Exper. Med., Suppl.*, 1921, **34**, 1), MOORE and others (*J. Am. Med. Assn.*, 1924, **82**, 528), LORENZ and others (*J. Am. Med. Assn.*, 1923, **80**, 1497), Stokes and Wilhelm and others. It is readily dissolved in 10 cc. of sterile water and administered intravenously by the syringe technique. The majority of investigators advised one injection every seven days in courses of ten injections followed by a rest interval of from four to six weeks. In many instances a second course of ten injections was given after the rest period. It is interesting to note that SOLOMON and VIETS (*J. Am. Med. Assn.*, 1925, **85**, 329) in their second report on tryparsamid advise as many as seventy-five injections before the best results can be expected. Stokes and Wilhelm used mercury between the tryparsamid injections, and felt that possibly their more favorable serologic results might be attributable to this combination. Haden and Wilson advised the use of mercury or bismuth along with tryparsamid. EBAUGH and DICKSON (*J. Am. Med. Assn.*, 1924, **83**, 803) used tryparsamid alone. Their serologic results, however, were not gratifying.

Indications. The low spirillicidal index of tryparsamid, as determined by Brown and Pearce, demonstrated that this drug was not adapted to the treatment of early types of syphilis. This phase was first studied clinically by MOORE, ROBINSON and LYMAN (*J. Am. Med. Assn.*, 1924, **83**, 888), who treated 10 cases of primary and secondary syphilis and 52 cases of tertiary syphilis. The latter group presented no clinical or serological evidence of neurosyphilis. In the primary group the lesions failed to heal; the spirochetes did not disappear from the primary lesions, and the blood Wassermann reaction was not affected. In the tertiary group, likewise, lesions failed to heal; the blood Wassermann remained unchanged. This evidence warranted the authors' conclusion that tryparsamid was without therapeutic effect in primary and secondary syphilis. Unlike the results observed in early syphilis, the response in neurosyphilis was very favorable; on this phase the majority of authors concentrated their experimental efforts. STOKES and WILHELM, SOLOMON and VIETS, MOORE, ROBINSON and KEIDEL, MOORE, ROBINSON and LYMAN, WILE and WIEDER (*J Am. Med. Assn.*, 1924, **83**, 1824; 1925, **84**, 1710), Lorenz and others, and many others advise the use of tryparsamid in neurosyphilis, especially in asymptomatic paresis, paresis (early) and taboparesis. Stokes and Wilhelm observed that treatment with tryparsamid in late, degenerative types of paresis frequently terminated fatally, although early response was encouraging. A review of the results of these investigators will follow.

Results. The unfavorable results of Moore, Robinson and Lyman in the treatment of early syphilis has already been mentioned, and the following reports deal with late syphilis only: Stokes and Wilhelm treated a total of 152 cases, of which 40 were cases confined to the

hospital for the insane and 112 were ambulatory. Forty of these cases carried a diagnosis of general paresis confirmed by clinical and serologic findings; 43 cases were of the asymptomatic paresis group and 14 were cases of tabes dorsalis with and without gastric crises. There were also 5 cases of multiple sclerosis treated with tryparsamid, the results of which were not gratifying. Results were based on a single course. Further improvement was, however, noted after a second or third course; that is, after a total of twenty to thirty injections. There was no symptomatic relief in the group with gastric crises. Wile and Wieder reported results obtained in the treatment of 85 cases of cerebrospinal syphilis, 32 of which were clear-cut general paresis, 12 taboparesis; 7 tabes dorsalis, 32 diffuse cerebrospinal syphilis and 1 acute syphilitic basilar meningitis. Moore, Robinson and Keidel treated 40 cases of neurosyphilis, 3 of which were early neurosyphilis, 27 general paresis, taboparesis, asymptomatic paresis and 10 meningovascular late syphilis. Lorenz and others reported the treatment of 88 cases of neurosyphilis. Seventy-eight of this group included asymptomatic paresis, genera paresis and taboparesis. There were also 10 cases of meningovascular late syphilis. SILVERSTON (*Lancet*, 1926, ii, 693) treated 18 cases of neurosyphilis, 15 of which were general paresis. BROWN and MARTIN (*Lancet*, 1926, ii, 699) reported the treatment of 17 cases of general paresis. Ebaugh and Dickson treated 52 cases of general paresis, 11 of which were of the advanced type. These authors agree with Stokes and Wilhelm that late degenerative types of paresis, while showing an early response to treatment, often terminate fatally. Moore, Robinson and Lyman reported the treatment of 133 cases of neurosyphilis. Solomon and Viets treated 100 cases of neurosyphilis with tryparsamid. Their best serologic results occured in tabetics.

Comparative Results. The following comparisons are confined to the group of asymptomatic paresis, general paresis, taboparesis and tabes dorsalis.

Clinical Improvement. Clinical improvement was reported by Stokes and Wilhelm as 47 per cent; Wile and Wieder, 26 per cent; Moore, Robinson and Keidel, 70 per cent; Lorenz and others, 78 per cent; Silverston, 70 per cent; Brown and Martin, 85 per cent; Ebaugh and Dickson, 36 per cent; Moore, Robinson and Lyman, 85 per cent; Solomon and Viets, nearly 100 per cent (second report).

Serologic Improvement. Stokes and Wilhelm reported the blood Wassermann reversed in 30 per cent and reduced in 9 per cent. Moore, Robinson and Keidel, 6.6 per cent and 20 per cent; Lorenz and others, 81 and 18 per cent. Stokes and Wilhelm reported the spinal fluid Wassermann negative in 17 per cent and reduced in 59 per cent; Wile and Wieder, 4.5 per cent (negative and reduced); Moore, Robinson and Keidel, 45 per cent and 40 per cent; Lorenz and others, 37 per cent and 51 per cent; Silverston, 25 per cent (negative only); Brown and Martin, 50 per cent (reduced only); Moore, Robinson and Lyman, 30 per cent and 82 per cent. Stokes and Wilhelm reported the cell count as negative in 81 per cent and reduced in 12 per cent; Wile and Wieder, 27 per cent (reduced only); Moore, Robinson and Keidel, 65 per cent and 20 per cent; Lorenz and others, 61 per cent and 38 per cent; Moore, Robinson and Lyman, 65 per cent and 85 per cent. Stokes and Wilhelm reported the globulin as negative in 23 per cent and reduced in

13 per cent; Wile and Wieder, 17 per cent (reduced only); Moore, Robinson and Keidel, 48 per cent and 18 per cent; Lorenz and others, 43 per cent and 50 per cent; Moore, Robinson and Lyman, 66 per cent (reduced only). Stokes and Wilhelm reported the colloidal-gold curve as negative in 36 per cent and reduced in 41 per cent; Wile and Wieder, 4 per cent (reduced only); Moore, Robinson and Keidel, 43 per cent and 26 per cent; Lorenz and others, 28 per cent and 53 per cent.

Complications. Visual disturbances, both subjective and objective, result from the use of tryparsamid, but they occur in such a small percentage as to be regarded as almost negligible. Care is advised, however, in its early administration; the development of objective disturbances is considered a contraindication of further medication by most observers. Tryparsamid in the treatment of neurosyphilis produced 10.2 per cent of subjective symptoms and 5.5 per cent objective according to Woods and Moore (*J. Am. Med. Assn.*, 1924, **82**, 2105). Only 33 per cent of a series of 12 cases with already existing syphilitic disease of the optic nerve developed visual disturbance while under treatment with tryparsamid. This altered the earlier views of these authors that syphilitic involvement of the optic nerve was an absolute contraindication to the use of the drug. Lillie (*J. Am. Med. Assn.*, 1924, **83**, 809) reported subjective visual disturbances occurring in 7.8 per cent and objective in 3.5 per cent. Smith (*J. Indiana Med. Assn.*, 1925, **18**, 125) reported 10 per cent of visual disturbances; Ebaugh and Dickson, 2 per cent; Lorenz, Loevenhart, Reitz and Eck (Am. J. Med. Sci., 1924, **168**, 157), 7 per cent; Crawford (*Canada Med. J.*, 1925, **15**, 47), 13.3 per cent; Stokes and Wilhelm found 2.6 per cent subjective and 5.4 per cent objective, 91 per cent of the subjective disturbances occurring within the first five injections. They found that if reactions did not develop during this time treatment could be carried on without danger, as they had given as many as three courses of the drug without effect. This is in accord with the more recent observations of Solomon and Viets. Cady and Alvis (*J. Am. Med. Assn.*, 1926, **86**, 184) studied 180 patients, of which 153 had normal eyes and 27 optic atrophy. Of the normal group, 5.2 per cent showed visual disturbances and 1.3 per cent actual damage which failed to involute following the withdrawal of the drug. Tryparsamid injected into rabbits to demonstrate its effect upon the eyes produced no ocular lesions, as showed in a thorough investigation carried out by Young and Loevenhart (*J. Pharm. and Exper. Therap.*, 1924, **23**, 107). Schwab and Cady (*Arch. Neurol. and Psychiat.*, 1925, **13**, 80), in a study of 97 patients receiving tryparsamid, recorded 30 per cent with subjective visual disturbances. None of these, however, suggested permanent damage. Other than eye complications were reported by Haden and Wilson, who noted the occurrence in their series of 2 cases of jaundice, 2 Herxheimer reactions and 1 case of dermatitis. These authors, however, remarked upon the low toxicity of the drug as one of its valuable assets. Silverston reported the occurrence of an early nitritoid reaction in 1 of his patients. He also observed 2 cases of jaundice.

OBSTETRICS

UNDER THE CHARGE OF
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The New Obstetric Forceps.—BARTON, CALDWELL and STUDDIFORD (*Am. J. Obst.*, 1928, **15**, 16) describes a modification of the already familiar Barton forceps. The angles between the blades have already been decreased and the length of the blade increased. They call attention to the uses of the instrument in rotating the fetal head high in the birth canal. They stress the fact that it is used more as a lever, and advise the use of the ordinary forceps as the easiest to effect the delivery after rotation has occurred.

Ovarian Dysfunction Dependent on Abnormalities of the Ductless Glands.—HIRST (*Am. J. Obst.*, 1928, **15**, 79) discussed this subject before the Chicago Gynecological Society because it was the most perplexing problem he has met in practice. His latest results are obtained in ovarian dysfunction by the injection of high doses of the sex hormone measured in rat units. He concludes that we are on the threshold of an addition to our therapeutic power.

Rupture of the Uterus in the Scar of a Previous Cesarean Section, Occurring in the Same Patient Within One Year.—GELPI (*Am. J. Obst.* 1928, **15**, 85) presents a case report in which the patient had a normal pregnancy first. The second child was born by section because of placenta previa. The third pregnancy resulted in rupture of the uterus which was repaired. Within a year the patient again became pregnant and again ruptured through her scar. Both times she was in a precarious condition but recovered the second time after a Porro operation.

The Alleged Synergism of Magnesium Sulphate and Morphin.—This is the reply of BECKMAN (*Am. J. Obst.*, 1928, **15**, 72) to Gwathmey's latest communication on this subject. He disagrees again with Gwathmey and concludes that this alleged synergism not only does not occur in man and experimentally does not take place in either rabbits or dogs.

Clinical Significance of the Sedimentation Test.—POLAK and TOLLEFSON (*J. Am. Med. Assn.*, 1928, **90**, 168) draw their conclusions from 1000 tests. Their conclusions are that it is an aid in diagnosis: (1) In determining the time for elective operation; (2) in prognosticating postoperative complications after the first week; (3) as a criterion for discharging patients. Finally a low reading means infection and a high reading means that infection can be excluded.

GYNECOLOGY

UNDER THE CHARGE OF

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Treatment of Chronic Gonorrhea.—There are some cases of chronic gonorrhea in the female which seem to defy all known methods of treatment, so that when an investigator publishes a method of treatment which has given satisfactory results after other methods have failed, we should at least give it consideration if not approval. LOESER (*Am. J. Obst. and Gynec.*, 1927, **14**, 329), of Berlin, proposes treating these cases by means of a single subcutaneous injection of live gonococci. He has had an experience of six years and concludes that patients suffering from chronic gonorrhea sustain this treatment without the slightest ill effect and a single injection might effect prompt cure of a chronic gonorrhea. Of the 118 cases unsuccessfully treated beforehand in various ways, 68 (about 60 per cent) recovered after a single injection. The gonococci for the injection are obtained from fresh pus, then grown on ascites agar and a pure culture obtained. They should be injected within forty-eight hours from the time they have been cultured, because the longer they live in the culture the more they lose their therapeutic efficiency. This treatment should be given only if the patient has not been treated in any manner during the preceding six to eight weeks, so as to be sure that the case is in the chronic stage, because recent treatment might cause an acute flare up. For the same reason the treatment should not be given during menstruation. Patients who have recently passed through other acute infectious diseases, that is, influenza, should be excluded from treatment. Just how this sort of treatment effects a cure is speculative, but the author assures us that there is no danger of septicemia from the injection of live organisms. Interesting and valuable as this form of treatment may be, it requires further verification before it can be generally recommended.

Treatment of Cervical Cancer.—At the Bellevue Hospital, in New York City, carcinoma of the cervix is not operated upon, states KAPLAN (*Radiology*, 1927, **9**, 314). Biopsy is done in every case, and the lesion is treated by disinfection of the local area, Roentgen ray therapy of the pelvis, radium therapy to the local lesion and radium puncture and endothermic surgery are performed when needed. The dosage of the irradiation varies with the histology and extent of the lesion, but the treatment is given with small doses over long periods of time. High-voltage Roentgen rays with heavy filtration and radium emanation in heavily filtered platinum tubes are used for the specific radiation therapy. The series of cases that he reports is too small and observed over too short a period of time to be considered here.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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Is Mastoidectomy Necessary in Young Children?—Believing that so many mastoid operations are performed in children because physicians have been taught to do them, and because they feel that under similar circumstances most other physicians do them, SCHWARTZ (*Arch. Otolaryngol.*, 1927, **6**, 353), after an extensive experience questions the advisability and necessity of operating to cure mastoiditis in the young. Following a comprehensive consideration of the anatomic peculiarities of the mastoid in young children, the author cites an illustrative case report. Holt's statistics regarding acute otitis media as it occurred at the New York Foundling Hospital are quoted: Here 573 cases of acute otitis were seen in five years, and of these acute mastoiditis was recognized in only 17 patients. There were only 2 examples of acute meningitis following otitis with mastoiditis; but there were 14 cases of acute meningitis from other causes. Of the 11 mastoid operations which were performed, six recovered and five died—all from causes directly associated with the operation. In view of the facts that: (1) The anatomy of the young child's mastoid differs in many important particulars from that of the adult. (2) Pronounced signs and symptoms in children under five or six years may be associated with mild infections, and do not necessarily of themselves mean that the condition is grave and alarming. (3) Recovery occurs in apparently serious cases after early incision of the drum, followed by adequate drainage (aided by suction, if necessary), and that sometimes vaccines and antisepsis of the nose and throat are helpful. (4) The hearing does not remain impaired, as is generally believed: the writer has come to the conclusion that the operation on the mastoid should not, as a rule, be performed on young children in acute cases. He adds that in infants up to the age of two years operations on the mastoid should practically never be performed; in those from two to five years of age, hardly ever; in those from five to twelve, rarely. In cases in which a subperiosteal abscess is present simple incision and drainage usually suffice, although when good drainage is obtained through the tympanic membrane, subperiosteal abscess rarely develops. When the infecting microörganism is Streptococcus mucosa capsulatus[1] or Streptococcus hemolyticus, operation is advisable after the eighth or tenth day (occasionally earlier), if severe symptoms and definite involvement of the mastoid are present.

Acute Otitis in Infants: Its Influence on Certain Systemic Conditions and the Influence of These Conditions on the Method of Treating the

[1] RETROSPECTOR'S NOTE.—An error. The accepted name is Streptococcus mucosus, an organism which usually exhibits sufficient biological characteristics to identify it as Pneumococcus mucosus (III).

Coëxisting Acute Otitis.—Emphasizing the importance of a close coöperation between the otologist and the pediatrician, DEAN (*Arch. Otolaryngol.*, 1927, **6**, 201) reports the observations on a series of infants suffering from acute otitis accompanied by marked systemic disturbances. After a review of the literature he discusses such systemic conditions caused by otitis, as refusal of food, malnutrition and loss of weight, cholera infantum, mastoiditis and syncopal attacks. Numerous case reports are cited to illustrate the various conditions described. In summary, he believes that the symptoms which lead to the discovery of otitis in infants are much more frequently pediatric than etiologic; that the conditions which determine the choice of treatment in otitis are oftener pediatric than otologic; that refusal of food, dehydration, diarrhea and loss of weight may be factors that will decide whether myringotomy should be performed; that they may indicate mastoidectomy. He says, however, that in the presence of these conditions a positive diagnosis of otitis should not be made unless an objective sign of the otitis exists, and avers that if otitis is present it can always be diagnosed. The disease may cause all the systemic conditions which he mentions in the article, except perhaps syncopal death. Inasmuch as paranasal sinus disease "unusually" coëxists with acute otitis, it is, as a rule, advisable to treat the patient for both, and it is often difficult to decide which is the most influential in causing the systemic disturbance. The point is made that the pediatrician should not confine his work to the general treatment of the child, but should enter actively into the discussion of the need of myringotomy or mastoidectomy. The author further says that "None of the conclusions are necessarily final, but they are interesting and important, and perhaps may contribute a little to the management of this difficult condition."

RADIOLOGY

UNDER THE CHARGE OF

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Physostigmin as an Aid in Gastrointestinal Roentgen Ray Diagnosis.—It is well known that gastrospasm may simulate various gastric lesions or interfere with the discovery of gastric lesions when they are present. RITVO and WEISS (*Am. J. Roentgenol. and Rad. Therap.*, 1927, **18**, 301) argue that lack of tone and sluggish or absent peristalsis may also cause misinterpretation of the roentgenologic findings or conceal lesions. Atropin has been used to overcome spasm, but, in the opinion of the writers, with only partial success, and they have sought for a drug which would not only eliminate spasm but at the same time would

increase tone and peristalsis. Physostigmin was selected for study and after experiments on animals it was administered orally to a series of patients in a dose of $\frac{1}{25}$ gr. (2.6 mg.). Increase of peristalsis, heightening of tonus and obliteration of spasm were manifest within five to fifteen minutes, and the action disappeared in forty minutes to two hours. Toxic manifestations occurred occasionally, but were not of sufficient severity to cause alarm. Weakness and headache are the earliest complaints. Sweating, cramps, nausea and vomiting are also early symptoms. Severe vomiting, abdominal pain and collapse are symptoms of marked intoxication. Atropin is the antagonist and offsets all symptoms rapidly and effectively.

Ultraviolet Radiation and the Calcium Factor in Normal and Pathologic States.—KIME (*Arch. Phys. Therap., X-ray, Rad.*, 1927, **8**, 509) regards ultraviolet radiation and calcium as synergists, since both stimulate the sympathetic nervous system and act along with catabolic endocrines. Both are indicated in all cases of low general metabolism, calcium insufficiency diseases and allergic phenomena. Allergic phenomena are chiefly due to the edema which is the result of increased endothelial permeability caused by parenteral proteins, and are specifically checked by ultraviolet radiation, calcium injections or catabolic endocrines and drugs. Ultraviolet, calcium and the catabolic synergists are contraindicated in advanced pulmonary tuberculosis, toxemias, fever, diabetes and toxic goiter.

Violet-ray Therapy of Furunculosis in Infants.—Furunculosis as a disease of infancy is fortunately rare, and occurs mostly in neglected infants and those of overcrowded asylums. It is a disease of white babies and occasionally of Mexicans, but almost never of negroes. In infants with low resistance there is frequently no rise of temperature, but if the child is in fairly good health very high fever may ensue. The clinical picture of severe furunculosis, according to BLATT (*Arch. Phys. Therap., X-ray, Rad.*, 1927, **8**, 520) is that of a daily crop of new lesions, deeply situated, easily palpable and, if untreated, breaking down into abscesses containing as much as 1 or 2 cc. of yellow or white pus. Many forms of treatment have been attempted in the past. Wet dressings macerate the skin without avail. Ointments of ammoniated mercury or ichthyol have been tried. The author has had best results from incising the lesions, expressing the pus and following with the violet rays. The scalp is treated first on one side and then on the other for from three to five minutes at a 15-inch distance. The child is then given a general treatment of short duration with the lamp at 20 inches. The involved area is then painted with mercurochrome. The process is repeated daily.

Importance of Roentgen Ray Examination of the Kidney in Case of Pain in the Upper Right Abdominal Quadrant.—NICHOLS (*Arch. Phys. Therap., X-ray, Rad.*, 1927, **8**, 493) points out that many diseases give rise to pain in the right upper abdominal quadrant; among them are lesions of the spine, disease of the gall bladder, pyloric or duodenal ulcer, cancer of the stomach, appendicitis, subdiaphragmatic pleurisy, angina pectoris, cancer of the colon and lesions of the kidney. Most

of the conditions cited present a rather characteristic clinical picture, and the diagnosis of many can easily be confirmed or excluded by roentgenologic examination. Diseases of the kidney, however, do not usually give a very clear-cut chain of clinical symptoms, and when the clinical facts cannot be definitely explained otherwise, the right kidney and ureter should always be examined with the Roentgen ray. The study of the kidney is best carried out by stereoscopic roentgenography, followed, if necessary, by pyelography.

Epiphyseolysis.—Bernstein and Arens (*Radiology*, 1927, **9**, 497) apply this term to spontaneous separation of the epiphysis of the femoral head, and they believe it is due to a constitutional disturbance perhaps of endocrine origin. A slight injury to the hip with gradually developing disability should lead one to suspect the presence of this condition. The outstanding physical finding is adduction and external rotation of the thigh. The Roentgen ray will confirm the diagnosis. The epiphyseal separation may be associated with epiphysitis elsewhere, such as at the knee joint. The writers believe that vertebral epiphysitis, infarction of the metatarsal head and Osgood's disease belong in the same group and probably have the same etiologic factor in common.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Etiology of Infantile Acquired Hemiplegia.—Ford and Schaffer (*Arch. Neurol. and Psychiat.*, 1927, **18**, 323) state that the liability to hemiplegia in the first decade is less than one-sixtieth of that in the seventh decade. Nevertheless, they were able to find 70 such hemiplegias among 50,000 case histories at the Harriet Lane Home. They give a rather extended review of the literature, dividing the cases into those which follow acute infectious diseases and those which occur in apparently healthy children. The hemiplegias following acute infectious diseases would seem to be due, in general, to vascular lesions according to the material which they were able to collect from the literature. The group occurring in apparently healthy children presents a more obscure etiology. The authors discuss the various theories already put forth. Strümpell's suggestion, that these hemiplegias were due to the same virus which causes poliomyelitis, they would discard on the basis of meager anatomic support. They admit the possibility that Heine-Medin disease may cause septic paralysis of hemiplegic distribution, but believe such cases to be extremely rare. Also on the basis of lack of pathologic findings they would rule out the idea that these hemiplegias are generally associated with epidemic encephalitis.

The relation of these hemiplegias to miscellaneous infections is not clear, but they have been found associated with tonsillitis, bronchitis, "croup," otitis media and septic sinus thrombosis due to otitis media, following mastoid operations, pyelitis, blood-stream infections with Staphylococcus aureus, pneumonia, erythema nodosum and severe enteritis. Congenital syphilis as a cause is much less frequent than one would suppose. A few cases have been described due to tuberculosis. A few cases have been attributed to convulsions, but the authors question whether the hemiplegia and the convulsions are not due to the same cause. Association with congenital vascular abnormalities and nonseptic sinus thrombosis is also excessively rare. The authors present an analysis of the 70 cases from the Harriet Lane Home. Excluding from these all cases associated with heart disease, meningitis, tumor of the brain, birth injury and abscess, they had 38 left which they considered belonged to the group under discussion. They found 5 more cases in the records of the medical department, giving them a total of 43. Sixteen of these followed immediately after some acute infectious disease. In 7 cases the onset was associated with some local infection. Syphilis was the etiologic factor in only 1 case. In 19 cases the children were considered healthy when the paralysis occurred. Spinal fluid examinations were normal in 9 of 10 fluids secured in the acute stage of the illness. In the other there were 10 cells and a doubtful globulin reaction. The pathologic anatomy of these hemiplegias following acute infectious diseases they find to be predominantly vascular in character. They state that the relative proportion of thrombosis, hemorrhage and embolism are different in different infections. Thus, in pertussis they found that cerebral hemorrhage is discovered in almost all cases, whereas only thrombosis of the cerebral arteries has been found in the few cases complicating typhoid fever and embolism is the commonest cause in diphtheria. In the group occurring in apparently healthy children very few autopsies have been performed. While hemorrhage is frequent, the cause for the hemorrhage usually cannot be found.

Obstruction of the Longitudinal Sinus.—Doyle (*Arch. Neurol. and Psychiat.*, 1927, **18**, 374) presents 4 cases, 1 following osteomyelitis of the skull, 1 following suppurative otitis media and 2 of unknown origin. All cases were followed by death and necropsy. He states that direct trauma and neoplasm may also result in occlusion of the sinus. In reviewing all the supratentorial operations performed at the Mayo Clinic between January 1, 1910, and October 15, 1926, the author found only 5 cases of sinus occlusion, all due to endotheliomas. The longitudinal sinus was exclusively involved in only 2 cases. He states that the occlusion may be asymptomatic unless it impairs the circulation of the large veins posterior to the Rolandic fissure. He concludes from his study of 4 cases: (1) In the absence of meningitis the early onset of apathy or stupor in a patient with evidence of thrombosis of the transverse sinus secondary to suppurative otitis media generally indicates infectious thrombosis of the superior longitudinal sinus, especially if associated with choked disks and convulsions. (2) When the probable presence of tumor or of inflammatory disease can be excluded, Jacksonian seizures progressing from one foot to the other or from a foot to

the homolateral arm; suggest probable thrombosis of the superior longitudinal sinus. (3) Abrupt onset of symptoms of increased intracranial pressure with fluctuating course suggest such thrombosis, as well as ventricular tumor. The absence of progression or actual regression of the symptoms favors thrombosis of the superior longitudinal sinus. If there is association with edema of the eyelids and dilatation of the veins of the eyelids and the forehead and if fracture of the skull, orbital and periorbital infections and thrombosis of the cavernous sinus can be excluded, the diagnosis is established.

Speech Defects in Children.—LIMA (*Ment. Hyg.*, 1927, **2**, 795) states that there are three causes of speech defects in children: (1) The environment in the sense of those factors which tend to prolong baby talk and lisping or those conditions that promote timidity, jealousy, shyness, and so forth; (2) physical disorders of various kinds; (3) nervous and mental disorders which cause a large percentage of speech defects. She believes that the discovery of these three factors by no means solves the problem, but that fortunately major speech defects are found only in a little more than 1 per cent of the public school enrollment. She states that Binet testing of children with speech defects shows the average intelligence of these children to be quite within the normal range. The speech defects found in the St. Paul school during one year were classified as follows:

Defects.	No. of cases.
Stuttering	122
Lisping	113
Letter substitution	103
Oral inactivity	22
Lateral lisp	11
Delayed speech	17
Nasality	4
Unusual accent	6
Organic malformations	4

Physical abnormalities associated with these defects included the following: Defective hearing, enlarged glands, malnutrition, defective teeth, diseased tonsils, defective nasal breathing and the various malformations of the jaw and palate. In 1922 42 per cent of all the speech cases enrolled in the St. Paul speech classes were underweight. The author states that it often happens that the speech defect vanishes when the physical defect is corrected, but that the contrary occurs just as frequently. She thinks we know least concerning nervous and mental diseases and emotional abnormalities in children with speech defects. The psychiatrist has helped little in this field, and the author quotes Brill as saying that out of 69 speech patients discharged by him as cured over a period of eleven years only 5 were permanently cured. She states that a surprising number of permanent cures are effected by trained speech teachers in the public schools among younger children, but gives no figures. A number of type cases are presented. Figures are given to show that the percentage of children with each type of speech defect differs with the age groups. Thus, letter substitution is a defect found mainly in the first and second grades, whereas stuttering increased in percentage until the high-school age, when it is practically the only defect noted.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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A Source of Error in Blood Typing.—The great importance of the correct determination of blood types before transfusion makes every source of error of interest. THOMSEN (*Compt. rend. Sc. de biol.*, 1927, **96**, 436) noted that on occasion Type I cells agglutinated as if they belonged to Type IV if the tests were not done at once but after eighteen to twenty-four hours. In investigating this phenomenon he discovered that the cells had become modified by some agent and were agglutinated by all four types of serum. FRIEDENREICH (*Idem.*, p. 1079) isolated from these cell suspensions a bacillus giving yellow colonies on agar and which could bring about this change in the red blood corpuscles. The transformation took place best at room temperature (15° C.), but not at 37° C., although the germs grew well at this temperature. He could not find evidence of the change under ten hours, but the speed of alteration depended on the numbers of bacteria added. He noted that the bacteria must be growing; he could not detect any visible alteration in the red cells and there was no hemolysis. Repeated washing of the modified cells did not alter their "panagglutinative" character. The blood cells of the newborn were not found to be affected, but all types of adult blood were. The modified cells were further shown to be able to remove by absorption the responsible substances. In a later paper (*Idem.*, 1927, **97**, 1266) he reported that filtrates of the culture of the bacillus brought about the same change in the red cells.

Aschoff-like Bodies in Myocardium in Meningococcus Infections.—The number of reported cases of infection with meningococcus in which the meninges are not involved is increasing. RHOADS (*Am. J. Path.*, 1927, **3**, 623) reports an interesting case of vegetative and ulcerative endocarditis in which the meningococcus was the infecting microörganism and lesions were found in the myocardium resembling those seen in rheumatic fever. Although the possibility of a previous attack of rheumatism was not completely ruled out, there was nothing in the past history suggesting such an attack and the lesions are looked upon as having been induced by the meningococcus.

Fusospirochetal Disease of the Lungs. Its Bacteriology, Pathology and Experimental Reproduction.—SMITH (*Am. Rev. Tuberc.*, 1927, **16**, 584) reports the results of a further study of 30 new cases, including a summary of the results obtained by other workers in 118 cases previously reported. He comes to the conclusion that a number of pul-

monary conditions, pulmonary gangrene, pulmonary abscess, certain types of unresolved pneumonias, bloody bronchitis, putrid bronchitis and primary bronchiectasis, which were formerly regarded as distinct entities, are in reality different manifestations of the same infection. The organisms constantly found in (1) the gums of patients suffering with these infections, (2) in washed sputum and (3) in diseased pulmonary tissue at necropsy are spirochetes, fusiform bacilli, cocci and vibrios. Pathologic examinations of lung abscess clearly show these organisms penetrating normal tissue, and lead him to believe they are primarily the cause of the abscess, rather than secondary invaders. By the introduction of material scraped from the alveolar border of the teeth in cases of moderately severe pyorrhea, into the trachea of anesthetized mice, guinea pigs and rabbits a variety of pulmonary infections resulted, which resembled very closely the acute and chronic manifestations of fusospirochetal disease in man. Pure cultures of Treponema microdentum, Treponema macrodentum and two types of fusiform bacilli have been isolated from washed pulmonary sputum.

Osteosclerotic Anemia Secondary to Epidermoid Carcinoma.—Rusk and Miles (*Am. J. Path.*, 1927, **3**, 289) report a case of a man with an epidermoid carcinoma, arising in the skin over the left molar region, giving rise to metastases in lungs and bones. The marrow had been practically obliterated by the carcinoma, resulting in multiple spontaneous fractures of the bones and a peculiar type of anemia associated with a myeloid reaction in the spleen. Twenty-three cases have been collected from the literature showing blood changes characteristic of the so-called osteosclerotic anemia. The outstanding features of the blood picture are: (1) A marked reduction in erythrocyte count with similar reduction in hemoglobin, with a resulting color index slightly under 1; (2) anisocytosis and poikilocytosis of the erythrocytes; (3) the appearance of immature red cells, both normoblasts and megaloblasts in the circulation; (4) appearance of myelocytes and less frequently myeloblasts in the circulation; (5) usually slight leukocytosis due principally to an increase in the myeloid series of white cells, though frequently there is a leukopenia; (6) frequently a terminal reduction in the blood platelet count. They believe that because of the complete absence of demonstrable lymph node or fascial plane involvement, the fact that the periosteal growths appeared younger than the metastases in the marrow cavity, and that frequently within the original periosteum strands of tumor cells could be seen extending like cords about capillaries, the carcinoma was carried to the bone marrow by the bloodstream and that the bone and periosteum became involved by extension from these metastases, the anemia in these cases being due to the widespread destruction of the erythroblastic tissues by the tumor growth and the accompanying desmoplasia. The burden of erythropoiesis is thrown hurriedly upon relatively small amounts of tissue, which liberate many immature and abnormal cells into the circulation. This case has the added feature of the myeloid reaction in the spleen which may be due to implants in the spleen of myeloid tissue from the bone marrow or reversion of the spleen to its embryonic functions.

HYGIENE AND PUBLIC HEALTH

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Bubonic Plague and Maritime Quarantine.—GRUBBS (*Pub. Health Repts.*, 1927, **42**, 2045) calls attention to the similarity of plague and yellow fever as respects maritime quarantine. The geographic limits of plague of the bubonic type at present are, in general, between 40° N. and 40° S. and the shores of the Mediterranean and Black Seas. It is true that the disease occasionally occurs outside of these limits, but it shows no tendency to become implanted or to assume epidemic proportions save within the the areas mentioned. This delimitation is regarded as due to the distribution of the Indian rat flea, Xenopsylla cheopis. A cheopis index is suggested as a means of determining the infectivity of a given port. It is shown that North American ports that have been infected have a larger number by far of Xenopsylla cheopis per rat than is the case in the cities in which plague has not been implanted. The rat is the most practicable point of attack in plague and the attack is best directed against the breeding of the animals. Fumigation alone is held to be uncertain and expensive in contrast with making conditions unfavorable for breeding. Rat-proofing of ships is urged as the most useful of antiplague measures as applied to vessels. Trapping and fumigation are of temporary value but more permanent measures are required. Rat-proofing of vessels is in practical use at the present time and is giving good results, though it is not expected that any vessel can be kept absolutely free of rats. What is necessary is accomplished if they are kept from breeding on the ship.

Two Cases of Rat-bite Fever.—RUBINO (*Pub. Health Repts.*, 1927, **42**, 2097) reports on 2 cases of rat-bite fever occurring in persons engaged in the capture of live rats for purposes of investigation. The diagnosis in each case was made on the characteristic clinical symptoms—intermittent relapsing fever, enlargement of regional lymph glands, eruption and response to neoarsphenamin, and, of course, the history of the bite.

Further Investigations on the Inheritance of Infectious Disease.—HIRZFELD and HIRZFELD (*Ztschr. f. Immunitatsforsch. u. exper. Therap.*, 1927, **54**, 81) studied 116 families with reference to the Schick reaction and blood grouping and 55 families with the Dick reaction. They found that where both parents are positive practically all the children are positive to both the Schick and Dick tests. In cases where both parents are negative, about one-third of the children are positive and

two-thirds negative. If one parent is positive and the other negative about one-half the children are positive. In comparing the middle class with the proletariat, they found a smaller number of positive children of negative parents among the latter group.

The Diphtheria Situation in Chicago.—BUNDESEN (*Pub. Health Repts.*, 1927, **42**, 2447) gives the following summary of his observations: "During the first seven months of this year 50 per cent more cases of and nearly 100 per cent more deaths from diphtheria have occurred in Chicago than were recorded for the corresponding months of 1926. This increase in the death rate from diphtheria has been due in part to a corresponding increase in morbidity, but the major factor has been a marked rise in the case fatality rate of the disease. Clinically, the type of diphtheria in Chicago this year is more malignant than that for several years past. The severe toxic and septic cases often fail to respond to treatment, even when antitoxin is given early and in usually adequate doses. The greater prevalence of diphtheria in Chicago during 1927 has not been due to infection by milk, food or epidemic foci, but represents a generalized increase in the endemic rate."

Should Scarlet Fever Isolation be Less Rigorous?—HOLST (*J. Prev. Med.*, 1927, **1**, 279) concludes from his experiences that there is no proof that isolation of scarlet fever in Norway has materially diminished the frequency of the disease. The data from Bergen and Trondhjem seem to indicate that the abolishment has had no bad effects. At the present time it cannot be decided whether or not the case fatality has been influenced by isolation. The author states that there is, therefore, no substantial reason for carrying on the practice of routine isolation of scarlet fever, which at present is milder even than measles and whooping cough. It is, however, of the greatest importance that the health authorities do not get out of touch with the disease, which, probably, at any time can revert to the old, malign type, thus making it again necessary to change measures.

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